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2. Patent application number *(The Patent Office will fill in this part)* 26 SEP 2003 0322534.9

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 Sodertalje
Sweden

Patents ADP number *(if you know it)* 07829448005

If the applicant is a corporate body, give the country/state of its incorporation Sweden

4. Title of the invention

QUINAZOLINE DERIVATIVES

5. Name of your agent *(if you have one)* Michael Andrew NELSON

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Global Intellectual Property
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Patents ADP number *(if you know it)* 08179707001

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

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Description	82
Claim(s)	5
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11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 25-09-03

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Jennifer Bennett - 01625 230148

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QUINAZOLINE DERIVATIVES

The invention concerns certain novel quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of said quinazoline derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

Many of the current treatment regimes for diseases resulting from the abnormal regulation of cellular proliferation such as psoriasis and cancer, utilise compounds that inhibit DNA synthesis and cellular proliferation. To date, compounds used in such treatments are generally toxic to cells however their enhanced effects on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to these cytotoxic anti-tumour agents are currently being developed, for example selective inhibitors of cell signalling pathways. These types of inhibitors are likely to have the potential to display an enhanced selectivity of action against tumour cells and so are likely to reduce the probability of the therapy possessing unwanted side effects.

Eukaryotic cells are continually responding to many diverse extracellular signals that enable communication between cells within an organism. These signals regulate a wide variety of physical responses in the cell including proliferation, differentiation, apoptosis and motility. The extracellular signals take the form of a diverse variety of soluble factors including growth factors as well as paracrine and endocrine factors. By binding to specific transmembrane receptors, these ligands integrate the extracellular signal to the intracellular signalling pathways, therefore transducing the signal across the plasma membrane and allowing the individual cell to respond to its extracellular signals. Many of these signal transduction processes utilise the reversible process of the phosphorylation of proteins that are involved in the promotion of these diverse cellular responses. The phosphorylation status of target proteins is regulated by specific kinases and phosphatases that are responsible for the regulation of about one third of all proteins encoded by the mammalian genome. As phosphorylation is such an important regulatory mechanism in the signal transduction process, it is therefore not surprising that aberrations in these intracellular pathways result in abnormal

cell growth and differentiation and so promote cellular transformation (reviewed in Cohen *et al*, Curr Opin Chem Biol, 1999, 3, 459-465).

It has been widely shown that a number of these tyrosine kinases are mutated to constitutively active forms and/or when over-expressed result in the transformation of a variety of human cells. These mutated and over-expressed forms of the kinase are present in a large proportion of human tumours (reviewed in Kolibaba *et al*, Biochimica et Biophysica Acta, 1997, 133, F217-F248). As tyrosine kinases play fundamental roles in the proliferation and differentiation of a variety of tissues, much focus has centred on these enzymes in the development of novel anti-cancer therapies. This family of enzymes is divided into two groups - receptor and non-receptor tyrosine kinases e.g. EGF Receptors and the SRC family respectively. From the results of a large number of studies including the Human Genome Project, about 90 tyrosine kinase have been identified in the human genome, of this 58 are of the receptor type and 32 are of the non-receptor type. These can be compartmentalised in to 20 receptor tyrosine kinase and 10 non-receptor tyrosine kinase sub-families (Robinson *et al*, Oncogene, 2000, 19, 5548-5557).

The receptor tyrosine kinases are of particular importance in the transmission of mitogenic signals that initiate cellular replication. These large glycoproteins, which span the plasma membrane of the cell possess an extracellular binding domain for their specific ligands (such as Epidermal Growth Factor (EGF) for the EGF Receptor). Binding of ligand results in the activation of the receptor's kinase enzymatic activity that is encoded by the intracellular portion of the receptor. This activity phosphorylates key tyrosine amino acids in target proteins, resulting in the transduction of proliferative signals across the plasma membrane of the cell.

It is known that the erbB family of receptor tyrosine kinases, which include EGFR, erbB2, erbB3 and erbB4, are frequently involved in driving the proliferation and survival of tumour cells (reviewed in Olayioye et al., EMBO J., 2000, 19, 3159). One mechanism in which this can be accomplished is by overexpression of the receptor at the protein level, generally as a result of gene amplification. This has been observed in many common human cancers (reviewed in Klapper et al., Adv. Cancer Res., 2000, 77, 25) such as breast cancer (Sainsbury et al., Brit. J. Cancer, 1988, 58, 458; Guerin et al., Oncogene Res., 1988, 3, 21; Slamon et al., Science, 1989, 244, 707; Klijn et al., Breast Cancer Res. Treat., 1994, 29, 73 and reviewed in Salomon et al., Crit. Rev. Oncol. Hematol., 1995, 19, 183), non-small cell lung cancers (NSCLCs) including adenocarcinomas (Cerny et al., Brit. J. Cancer, 1986, 54,

265; Reubi et al., Int. J. Cancer, 1990, 45, 269; Rusch et al., Cancer Research, 1993, 53, 2379; Brabender et al, Clin. Cancer Res., 2001, 7, 1850) as well as other cancers of the lung (Hendler et al., Cancer Cells, 1989, 7, 347; Ohsaki et al., Oncol. Rep., 2000, 7, 603), bladder cancer (Neal et al., Lancet, 1985, 366; Chow et al., Clin. Cancer Res., 2001, 7, 1957, Zhau et al., Mol Carcinog., 3, 254), oesophageal cancer (Mukaida et al., Cancer, 1991, 68, 142), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen et al., Oncogene Res., 1987, 1, 149; Kapitanovic et al., Gastroenterology, 2000, 112, 1103; Ross et al., Cancer Invest., 2001, 19, 554), cancer of the prostate (Visakorpi et al., Histochem. J., 1992, 24, 481; Kumar et al., 2000, 32, 73; Scher et al., J. Natl. Cancer Inst., 2000, 92, 1866), leukaemia (Konaka et al., Cell, 1984, 37, 1035, Martin-Subero et al., Cancer Genet Cytogenet., 2001, 127, 174), ovarian (Hellstrom et al., Cancer Res., 2001, 61, 2420), head and neck (Shiga *et al.*, Head Neck, 2000, 22, 599) or pancreatic cancer (Ovotny et al., Neoplasma, 2001, 48, 188). As more human tumour tissues are tested for expression of the erbB family of receptor tyrosine kinases it is expected that their widespread prevalence and importance will be further enhanced in the future.

As a consequence of the mis-regulation of one or more of these receptors, it is widely believed that many tumours become clinically more aggressive and so correlate with a poorer prognosis for the patient (Brabender et al, Clin. Cancer Res., 2001, 7, 1850; Ross et al, Cancer Investigation, 2001, 19, 554, Yu et al., Bioessays, 2000, 22.7, 673). In addition to these clinical findings, a wealth of pre-clinical information suggests that the erbB family of receptor tyrosine kinases are involved in cellular transformation. This includes the observations that many tumour cell lines overexpress one or more of the erbB receptors and that EGFR or erbB2 when transfected into non-tumour cells have the ability to transform these cells. This tumourigenic potential has been further verified as transgenic mice that overexpress erbB2 spontaneously develop tumours in the mammary gland. In addition to this, a number of pre-clinical studies have demonstrated that anti-proliferative effects can be induced by knocking out one or more erbB activities by small molecule inhibitors, dominant negatives or inhibitory antibodies (reviewed in Mendelsohn et al., Oncogene, 2000, 19, 6550). Thus it has been recognised that inhibitors of these receptor tyrosine kinases should be of value as a selective inhibitor of the proliferation of mammalian cancer cells (Yaish *et al.* Science, 1988, 242, 933, Kolibaba *et al*, Biochimica et Biophysica Acta, 1997, 133, F217-F248; Al-Obeidi *et al*, 2000, Oncogene, 19, 5690-5701; Mendelsohn *et al*, 2000, Oncogene, 19, 6550-6565). In addition to this pre-clinical data, findings using inhibitory antibodies against EGFR and erbB2

(c-225 and trastuzumab respectively) have proven to be beneficial in the clinic for the treatment of selected solid tumours (reviewed in Mendelsohn *et al*, 2000, Oncogene, 19, 6550-6565).

Amplification and/or activity of members of the erbB type receptor tyrosine kinases have been detected and so have been implicated to play a role in a number of non-malignant proliferative disorders such as psoriasis (Ben-Bassat, Curr. Pharm. Des., 2000, 6, 933; Elder et al., Science, 1989, 243, 811), benign prostatic hyperplasia (BPH) (Kumar et al., Int. Urol. Nephrol., 2000, 32,73), atherosclerosis and restenosis (Bokemeyer et al., Kidney Int., 2000, 58, 549). It is therefore expected that inhibitors of erbB type receptor tyrosine kinases will be useful in the treatment of these and other non-malignant disorders of excessive cellular proliferation.

European patent application EP 566 226 discloses certain 4-anilinoquinazolines that are receptor tyrosine kinase inhibitors.

International patent applications WO 96/33977, WO 96/33978, WO 96/33979, WO 96/33980, WO 96/33981, WO 97/30034, WO 97/38994 disclose that certain quinazoline derivatives which bear an anilino substituent at the 4-position and a substituent at the 6- and/or 7- position possess receptor tyrosine kinase inhibitory activity.

European patent application EP 837 063 discloses aryl substituted 4-aminoquinazoline derivatives carrying moiety containing an aryl or heteroaryl group at the 6-or 7- position on the quinazoline ring. The compounds are stated to be useful for treating hyperproliferative disorders.

International patent applications WO 97/30035 and WO 98/13354 disclose certain 4-anilinoquinazolines substituted at the 7- position are vascular endothelial growth factor receptor tyrosine kinase inhibitors.

WO 00/55141 discloses 6,7-substituted 4-anilinoquinazoline compounds characterised in that the substituents at the 6-and/or 7-position carry an ester linked moiety (RO-CO).

WO 00/56720 discloses 6,7-dialkoxy-4-anilinoquinazoline compounds for the treatment of cancer or allergic reactions.

WO 02/41882 discloses 4-anilinoquinazoline compounds substituted at the 6- and/or 7- position by a substituted pyrrolidinyl-alkoxy or piperidinyl-alkoxy group.

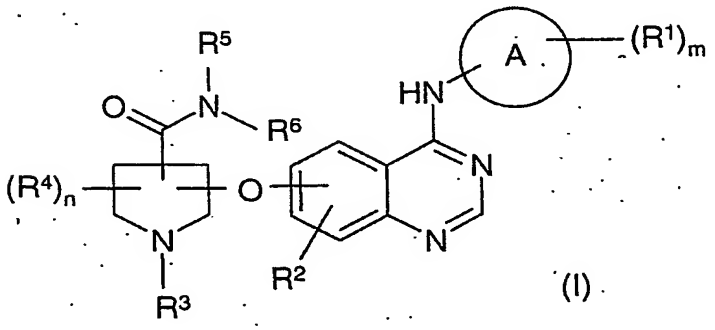
We have now surprisingly found that certain pyrrolidinyloxyquinazoline derivatives possess potent anti-tumour activity and in general have good physical properties, for example good solubility.

Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of one or more of the erbB family of receptor tyrosine kinases that are involved in the signal transduction steps which lead to the proliferation of tumour cells. In particular, it is believed that the compounds of the present invention provide an anti-tumour effect by way of inhibition of EGFR and/or erbB2 receptor tyrosine kinases.

Generally the compounds of the present invention possess potent inhibitory activity against the erbB receptor tyrosine kinase family, for example by inhibition of EGFR and/or erbB2 and/or erbB4 receptor tyrosine kinases, whilst possessing less potent inhibitory activity against other kinases. Furthermore, certain compounds of the present invention possess substantially better potency against the EGFR over that of the erbB2 tyrosine kinase. The invention also includes compounds that are active against all or a combination of EGFR, erbB2 and erbB4 receptor tyrosine kinases, thus potentially providing treatments for conditions mediated by one or more of these receptor tyrosine kinases.

Generally the compounds of the present invention exhibit favourable physical properties such as a high solubility whilst retaining high antiproliferative activity. Furthermore, many of the compounds according to the present invention are inactive or only weakly active in a hERG assay.

According to a first aspect of the invention there is provided a quinazoline derivative of the Formula (I):



(I)

wherein:

either R^2 is in the 6-position and the substituted-pyrrolidinyloxy group is in the 7-position of the quinazoline ring or R^2 is in the 7-position and the substituted-pyrrolidinyloxy group is in the 6-position of the quinazoline ring;

A is phenyl or pyridyl;

each $\mathbf{R^1}$ is a substituent on a ring carbon atom in ring A and is independently selected from halogeno, cyano, nitro, hydroxy, carboxy, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkoxycarbonyl, ureido, N-(1-6C)alkylureido, N,N-di-[(1-6C)alkyl]ureido, $-NR^aR^b$, $-SO_2NR^aR^b$ and a group of the formula $-CONR^aR^b$ (wherein $\mathbf{R^a}$ is hydrogen or (1-6C)alkyl and $\mathbf{R^b}$ selected from hydrogen, (1-6C)alkyl, phenyl, benzyl, heterocyclyl, heterocyclyl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, (3-7)cycloalkyl and (3-7)cycloalkyl(1-3C)alkyl wherein any alkyl, heterocyclyl, heteroaryl and cycloalkyl groups in R^a and R^b are optionally substituted by 1, 2 or 3 substituents selected from (1-4C)alkyl, halogeno, hydroxy and (1-4C)alkoxy;

or $\mathbf{R^a}$ and $\mathbf{R^b}$ together with the nitrogen atom to which they are attached form a 4, 5 or 6-membered ring which optionally contains an additional ring heteroatom selected from nitrogen, oxygen and sulphur and which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from halogeno, hydroxy, (1-4C)alkyl and (1-3C)alkylenedioxy and optionally substituted on any available ring nitrogen by a substituent selected from (1-4C)alkyl and (2-4C)alkanoyl (provided the ring is not thereby quaternised), and wherein any (1-4C)alkyl or (2-4C)alkanoyl group present as a substituent on the ring formed by R^a and R^b together with the nitrogen atom to which they are attached is optionally substituted by 1, 2 or 3 substituents independently selected from halogeno, hydroxyl, (1-4C)alkyl and (1-4C)alkoxy;)

or, when two $\mathbf{R^1}$ groups are attached to adjacent carbon atoms, they may, together with the carbon atoms to which they are attached, form a pyrrole ring, wherein the pyrrole ring is optionally substituted by 1 or 2 substituents independently selected from (1-6C)alkyl, halogeno, cyano, nitro, hydroxy, amino, carbamoyl, sulfamoyl and trifluoromethyl;

or, when two $\mathbf{R^1}$ groups are attached to adjacent carbon atoms, they may, together form a (1-3C)alkylenedioxy group $[-O(CH_2)_{0-3}O]$;

m is 0, 1, 2 or 3;

each R^2 is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-3C)alkyl and a group of the formula R^7O-, wherein R^7 is (1-6C)alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy and a group of the formula R^8O- (wherein R^8 is (1-3C)alkyl);

R^3 is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-3C)alkyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (2-6C)alkanoyl, carbamoyl(1-6C)alkyl, N-(1-6C)alkylcarbamoyl(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl(1-6C)alkyl, sulfamoyl(1-6C)alkyl, N-(1-6C)alkylsulfamoyl(1-6C)alkyl, N,N-di-[(1-6C)alkyl]sulfamoyl(1-6C)alkyl and (2-6C)alkanoyl(1-6C)alkyl,

and wherein any (1-6C)alkyl or (2-6C)alkanoyl group within R^3 is optionally substituted by 1, 2 or 3 substituents independently selected from halogeno, hydroxy and (1-6C)alkyl and/or optionally a substituent selected from cyano, nitro, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy and NR^cR^d, wherein R^c is hydrogen or (1-4C)alkyl and R^d is hydrogen or (1-4C)alkyl, and wherein any (1-4C)alkyl in R^c or R^d is optionally substituted by 1, 2 or 3 substituents independently selected from halogeno and hydroxy and/or optionally a substituent selected from cyano, nitro and (1-4C)alkoxy,

or R^c and R^d together with the nitrogen atom to which they are attached form a 4, 5 or 6 membered ring which optionally contains an additional ring heteroatom selected from nitrogen, oxygen and sulphur and which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from halogeno, hydroxy, (1-4C)alkyl and (1-3C)alkylenedioxy, and optionally substituted on any available ring nitrogen by a substituent selected from (1-4C)alkyl and (2-4C)alkanoyl (provided the ring is not thereby quaternised),

and wherein any (1-4C)alkyl or (2-4C)alkanoyl group present as a substituent on the ring formed by R^c and R^d together with the nitrogen atom to which they are attached is optionally substituted by 1, 2 or 3 substituents independently selected from halogeno and hydroxy and/or optionally a substituent selected from (1-4C)alkyl and (1-4C)alkoxy;

each R^4 is independently selected from (1-4C)alkyl, (1-4C)alkoxy, cyano, halogeno, hydroxyl and oxo;

n is 0, 1 or 2;

R^5 is hydrogen or (1-6C)alkyl;

R^6 is selected from hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (3-7)cycloalkyl, (C1-6)alkylsulfonyl, heterocyclyl, heteroaryl, (3-7)cycloalkyl(1-3C)alkyl, (3-7)heterocyclyl(1-3C)alkyl and heteroaryl(1-3C)alkyl,

and wherein any (1-3C)alkyl, (1-6C)alkyl, (3-7)cycloalkyl, heteroaryl or heterocyclyl group within R^5 or R^6 is optionally substituted (on any available carbon atoms) by 1, 2 or 3 substituents independently selected from halogeno, hydroxy(1-6C)alkyl, (1-6C)alkoxycarbonyl, carbamoyl, (2-6C)alkanoylamino and hydroxy and/or optionally a substituent selected from oxo, cyano, nitro and (1-4C)alkoxy,

and wherein any heterocyclyl group within R^6 is optionally substituted on any available ring nitrogen (provided the ring is not thereby quaternised) by (1-4C)alkyl or (2-4C)alkanoyl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 4, 5 or 6 membered ring which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from halogeno, hydroxy, (1-4C)alkyl and (1-3C)alkylenedioxy, and optionally substituted on any available ring nitrogen by a substituent selected from (1-4C)alkyl and (2-4C)alkanoyl (provided the ring is not thereby quaternised),

and wherein any (1-4C)alkyl or (2-4C)alkanoyl group present as a substituent on the ring formed by R^5 and R^6 together with the nitrogen atom to which they are attached is optionally substituted by 1, 2 or 3 substituents independently selected from halogeno and hydroxy and/or optionally a substituent selected from (1-4C)alkyl and (1-4C)alkoxy;

provided that when the pyrrolidinyloxy group is linked to the 6-position of the quinazoline ring, m is 2 and substituents R^1 are both halogeno and attached to the 2- and 3- positions of the ring A, then R^6 is selected from substituted-(1-6C)alkyl (wherein substituted-(1-6C)alkyl is (1-6C)alkyl substituted by 1, 2 or 3 substituents independently selected from halogeno, hydroxy(1-6C)alkyl, (1-6C)alkoxycarbonyl, carbamoyl, (2-6C)alkanoylamino and hydroxy and/or optionally a substituent selected from oxo, cyano, nitro and (1-4C)alkoxy), (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (3-7)cycloalkyl, (C1-6)alkylsulfonyl, (3-7)heterocyclyl, heteroaryl, (3-7)cycloalkyl(1-6C)alkyl, (3-7)heterocyclyl(1-6C)alkyl and heteroaryl(1-6C)alkyl,

and wherein any (3-7)cycloalkyl, heteroaryl or (3-7)heterocyclyl group within R^5 or R^6 is optionally substituted (on any available carbon atoms) by 1, 2 or 3 substituents independently selected from halogeno, hydroxy(1-6C)alkyl, (1-6C)alkoxycarbonyl, carbamoyl, (2-

6C)alkanoylamino and hydroxy and/or optionally a substituent selected from oxo, cyano, nitro and (1-4C)alkoxy,

and wherein any heterocyclyl group within R^6 is optionally substituted on any available ring nitrogen (provided the ring is not thereby quaternised) by (1-4C)alkyl or (2-4C)alkanoyl, or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4, 5 or 6 membered ring which is substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from (1-3C)alkylenedioxy;

or a pharmaceutically-acceptable salt thereof.

The definitions of the variables given hereinabove will be referred to as definition 'I' for the purposes of defining classes of compound in Table A hereinbelow.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino and cyclohexylamino, and di-[(1-6Calkyl]amino includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetrically substituted carbon and/or sulfur atoms, and accordingly may exist in, and be isolated as enantiomerically pure, a mixture of diastereoisomers or as a racemate. The present invention includes in its definition any racemic, optically-active, enantiomerically pure, mixture of diastereoisomers, stereoisomeric form of the compound of Formula (I), or mixtures thereof, which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

The invention relates to all tautomeric forms of the compounds of the Formula I that possess antiproliferative activity.

It is also to be understood that certain compounds of the Formula I may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms, which possess antiproliferative activity.

It is also to be understood that certain compounds of the Formula I may exhibit polymorphism, and that the invention encompasses all such forms which possess antiproliferative activity.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for (3-7C)cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl.

A heterocyclyl group is a non-aromatic saturated (i.e. with the maximum degree of saturation) or partially saturated (i.e. ring systems retaining some, but not the full, degree of unsaturation) 3 to 7 membered monocyclic ring with up to 3 heteroatoms selected from oxygen, nitrogen and sulfur (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom, or a ring nitrogen atom (provided the ring is not thereby quaternised). Suitable values for heterocyclyl include for example, oxiranyl, oxetanyl, azetidinyl, tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, oxazepanyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, tetrahydrothienyl, tetrahydrothiopyranyl, thiomorpholinyl, more specifically including for example, tetrahydrofuran-3-yl, tetrahydrofuran-2-yl-, tetrahydropyran-4-yl, tetrahydrothien-3-yl, tetrahydrothiopyran-4-yl, pyrrolidin-3-yl, pyrrolidin-2-yl, 3-pyrrolin-3yl-, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-4-yl, piperidin-3-yl, piperidin-2-yl, homopiperidin-3-yl, homopiperidin-4-yl, piperazin-1-yl, 1,4-oxazepanyl, or 1,2,3,6-tetrahydropyridin-4-yl. A nitrogen or sulfur atom within a heterocyclyl group may be oxidized to give the corresponding N or S oxide(s), for example 1,1-dioxotetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothiopyranyl or 1-oxotetrahydrothiopyranyl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-oxopiperazinyl, 2-thioxopyrrolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl or 2,6-dioxopiperidinyl.

Particular values forheterocyclyl include, for example, non-aromatic saturated or partially saturated 3 to 7 membered monocyclic heterocyclyl rings with 1 ring nitrogen or sulfur heteroatom and optionally 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur. Examples of such rings include azetidinyl, oxazepanyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, tetrahydrothienyl, tetrahydrothiopyranyl or thiomorpholinyl.

Further particular values for heterocyclyl include, for example, morpholino, or 4, 5 or 6 membered heterocyclyl rings containing 1 nitrogen atom and optionally 1 heteroatom selected from nitrogen and sulfur such as piperazinyl, pyrrolidinyl, piperidinyl, particularly pyrrolidin-1-yl, pyrrolidin-2-yl, piperazin-1-yl, piperidino, morpholino or piperazino.

When R^a and R^b or R^c and R^d or R^5 and R^6, together with the nitrogen atom to which they are attached form a 4, 5 or 6 membered ring, the ring is a saturated or partially saturated non-aromatic heterocyclyl ring containing 1 nitrogen and optionally 1 heteroatom selected from oxygen, sulfur and nitrogen and wherein the ring so formed is linked via a ring nitrogen atom to the group to which the ring is attached. Suitable values for R^a and R^b or R^c and R^d or R^5 and R^6, when together with the nitrogen atom to which they are attached form a 4, 5 or 6 membered ring include, for example, azetidin-1-yl, pyrrolin-1-yl, 1,2,3,6-tetrahydropyridin-1-yl, pyrrolidin-1-yl, piperidino, piperazin-1-yl and morpholino.

A heteroaryl ring is a monocyclic, 5- or 6- memebered aryl ring containing 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of heteroaryl rings include pyrazolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidyl, furanyl, pyrazolyl, thiazolyl, isothiazolyl and thiadiazolyl.

Suitable values for any of the R^1, R^2, R^3, R^4, R^5, R^6 or for various groups within them as defined hereinbefore or hereafter in this specification include:-

for halogeno	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl, tert-butyl, pentyl and hexyl;
for (1-4C)alkyl:	methyl, ethyl, propyl, isopropyl and tert-butyl;
for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (2-8C)alkenyl:	vinyl, isopropenyl, allyl and but-2-enyl;
for (2-8C)alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for (2-6C)alkenyloxy:	vinyloxy and allyloxy;

for (2-6C)alkynyloxy: ethynyloxy and 2-propynyloxy;

for (1-6C)alkylthio: methylthio, ethylthio and propylthio;

for (1-6C)alkylsulfinyl: methylsulfinyl and ethylsulfinyl;

for (1-6C)alkylsulfonyl: methylsulfonyl and ethylsulfonyl;

for (1-6C)alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;

for (2-6C)alkanoyl: acetyl, propionyl and isobutyryl;

for (2-6C)alkanoyloxy: acetoxy and propionyloxy;

for (2-6C)alkanoylamino: acetamido and propionamido;

for N-(1-6C)alkyl-(2-6C)alkanoylamino: N-methylacetamido and N-methylpropionamido;

for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;

for hydroxy-(1-6C)alkoxy: hydroxymethoxy, 2-hydroxyethoxy, 1-hydroxyethoxy and 3-hydroxypropoxy;

for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;

for carbamoyl(1-6C)alkyl: carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl and 3-carbamoylpropyl;

for N-(1-6C)alkylcarbamoyl(1-6C)alkyl: N-methylcarbamoylmethyl, N-ethylcarbamoylmethyl, N-propylcarbamoylmethyl, 1-(N-methylcarbamoyl)ethyl, 2-(N-methylcarbamoyl)ethyl and 3-(N-methylcarbamoyl)propyl;

for N,N di-(1-6C)alkylcarbamoyl(1-6C)alkyl: N,N-dimethylcarbamoylmethyl, N,N-diethylcarbamoylmethyl, N methyl,N-ethylcarbamoylmethyl, 1-(N,N-dimethylcarbamoyl)ethyl, 1-(N,N-diethylcarbamoyl)ethyl, 2-(N,N-dimethylcarbamoyl)ethyl, 2-(N,N-diethylcarbamoyl)ethyl and 3-(N,N-dimethylcarbamoyl)propyl;

for sulfamoyl(1-6C)alkyl:	sulfamoylmethyl, 1-sulfamoylethyl, 2-sulfamoylethyl and 3-sulfamoylpropyl;
for N-(1-6C)alkylsulfamoyl(1-6C)alkyl:	N-methylsulfamoylmethyl, N-ethylsulfamoylmethyl, N-propylsulfamoylmethyl, 1-(N-methylsulfamoyl)ethyl, 2-(N-methylsulfamoyl)ethyl and 3-(N-methylsulfamoyl)propyl;
for N,N di-(1-6C)alkylsulfamoyl(1-6C)alkyl:	N,N-dimethylsulfamoylmethyl, N,N-diethylsulfamoylmethyl, N methyl,N-ethylsulfamoylmethyl, 1-(N,N-dimethylsulfamoyl)ethyl, 1-(N,N-diethylsulfamoyl)ethyl, 2-(N,N-dimethylsulfamoyl)ethyl, 2-(N,N-diethylsulfamoyl)ethyl and 3-(N,N-dimethylsulfamoyl)propyl;
for (2-6C)alkanoyl(1-6C)alkyl:	acetylmethyl, propionylmethyl, 2-acetylethyl and 2-propionylethyl;
for N-(1-6C)alkylureido:	N-methylureido, N-ethylureido and N-propylureido;
for N,N-[di(1-6C)]alkylureido:	N,N-(dimethyl)ureido, N-methyl-N-ethylureido and N-methyl-N-propylureido;
for (3-7C)cycloakyl;	cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; and
for (3-7C)cycloakyl(1-3C)alkyl;	cyclopropylmethyl, 2-cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

Examples of suitable groups for $-CONR^aR^b$ in R^1 are: carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl and N-isopropylcarbamoyl, N-isobutylcarbamoyl, N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N,N-diethylcarbamoyl, N-isobutyl-N-methylcarbamoyl, N-phenylcarbamoyl, N-phenyl-N-methylcarbamoyl, N-cyclopentylcarbamoyl; N-cyclohexylyl-N-methylcarbamoyl; N-(2-methoxytheyl)-N-methylcarbamoyl, 2-hydroxypyrrolidin-1-ylcarbonyl, morpholinocarbonyl and 1,2,36-tetrahydropyridin-1-ylcarbonyl.

Examples of suitable groups for $-SO_2NR^aR^b$ in R^1 are: sulfamoyl, N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl and N-isopropylsulfamoyl, N-isobutylsulfamoyl, N,N-dimethylsulfamoyl, N-ethyl-N-methylsulfamoyl, N,N-diethylsulfamoyl, N-isobutyl-N-methylsulfamoyl, N-phenylsulfamoyl, N-phenyl-N-methylsulfamoyl, N-cyclopentylsulfamoyl; N-cyclohexylyl-N-methylsulfamoyl; N-(2-methoxytheyl)-N-methylsulfamoyl, 2-hydroxypyrrolidin-1-ylsulfonyl, morpholinosulfonyl and 1,2,36-tetrahydropyridin-1-ylsulfonyl.

Examples of suitable groups for NR^aR^b in R^1 include amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, dimethylamino, diethylamino, N-ethyl-N-methylamino, diisopropylamino, N-isobutyl-N-methylamino, N-phenylamino, N-iphenyl-N-methylamino, N-cyclopentylamino, N-cyclopentyl-N-methylamino, N-cyclohexylamino, N-cyclohexyl-N-methylamino, N-cyclohexyl-N-methylamino, N-[2-(hydroxyethyl)]amino, N-[2-(hydroxyethyl)]-N-methylamino, N-(furan-2-yl)amino, N-(furan-2-yl)-N-methylamino, azetidin-1-yl, pyrrolin-1-yl, pyrrolidin-1-yl, piperidino, morpholino and piperazino ring.

A suitable value for a (1-3C)alkylenedioxy group which may be present as a substituent formed by 2 R^1 groups on ring A or on the ring formed by R^a and R^b or R^5 and R^6 together with the nitrogen atom to which they are attached is, for example, methylenedioxy, ethylidenedioxy, isopropylidenedioxy or ethylenedioxy and the oxygen atoms thereof occupy adjacent ring positions. A particular value for a (1-3C)alkylenedioxy group which may be present as a substituent formed by 2 R^1 groups on ring A or on the ring formed by R^a and R^b or R^5 and R^6 together with the nitrogen atom to which they are attached is methylenedioxy.

It is to be understood that when, R^1 is a group (1-6C)alkyl substituted by, for example amino to give for example a 2-aminoethyl group, it is the (1-6C)alkyl group that is attached to ring A. An analogous convention applies to the other groups defined herein.

When in this specification reference is made to a (1-4C)alkyl group it is to be understood that such groups refer to alkyl groups containing up to 4 carbon atoms. A skilled person will realise that representative examples of such groups are those listed above under (1-6C)alkyl that contain up to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl and tert-butyl. Similarly, reference to a (1-3C)alkyl group refers to alkyl groups containing up to 3 carbon atoms such as methyl, ethyl, propyl and isopropyl. A similar convention is adopted for the other groups listed above such as (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl and (2-4C)alkanoyl.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulfuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, quinazoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of m, R^1, R^2, R^3, R^4, R^5, R^6, A, m and n has any of the meanings defined hereinbefore or in paragraphs listed hereinafter:-

1. Definitions of m and R^1

(a) m is 0, 1, 2 or 3 and R^1 is independently selected from halogeno, cyano, nitro, hydroxy, trifluoromethyl, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, ureido, N-(1-6C)alkylureido, N,N-di-[(1-6C)alkyl]ureido, $-NR^aR^b$, $-SO_2NR^aR^b$ and a group of the formula $-CONR^aR^b$ (wherein R^a and R^b are as hereinabove defined);

or, when two R^1 groups are attached to adjacent carbon atoms, they may, together with the carbon atoms to which they are attached, form a pyrrole ring, wherein the pyrrole ring is optionally substituted by 1 or 2 substituents independently selected from (1-6C)alkyl, halogeno, cyano, nitro, hydroxy, amino, carbamoyl, sulfamoyl and trifluoromethyl;

or, when two R^1 groups are attached to adjacent carbon atoms, they may, together form a (1-3C)alkylenedioxy group.

(b) m is 0, 1, 2 or 3 and R^1 is independently selected from halogeno, cyano, nitro, hydroxy, trifluoromethyl, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, ureido, N-(1-6C)alkylureido, N,N-di-[(1-6C)alkyl]ureido, $-NR^aR^b$, $-SO_2NR^aR^b$ and a group of the formula $-CONR^aR^b$ (wherein R^a is hydrogen or (1-6C)alkyl and R^b selected from hydrogen, (1-6C)alkyl, (3-7)cycloalkyl, heteroaryl and wherein any alkyl, (3-7)cycloalkyl, heteroaryl in R^a and R^b are optionally substituted by 1 or 2 substituents selected from hydroxy and (1-4C)alkoxy;

or R^a and R^b together with the nitrogen atom to which they are attached form a 4, 5 or 6-membered ring which optionally contains an additional ring heteroatom selected from nitrogen, oxygen and sulphur and which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from halogeno, hydroxy, (1-4C)alkyl and (1-3C)alkylenedioxy and optionally substituted on any available ring nitrogen by a substituent selected from (1-4C)alkyl and (2-4C)alkanoyl (provided the ring is not thereby quaternised), and wherein any (1-4C)alkyl or (2-4C)alkanoyl group present as a substituent on the ring formed by R^a and R^b together with the nitrogen atom to which they are attached is optionally substituted by 1, 2 or 3 substituents independently selected from hydroxyl and (1-4C)alkoxy);
or, when two R^1 groups are attached to adjacent carbon atoms, they may, together with the carbon atoms to which they are attached, form a pyrrole ring, wherein the pyrrole ring is optionally substituted by 1 or 2 substituents independently selected from hydroxy;
or, when two R^1 groups are attached to adjacent carbon atoms, they may, together form a (1-3C)alkylenedioxy group.

(c) m is 0, 1, 2 or 3 and R^1 is independently selected from halogeno, (1-6C)alkyl, trifluoromethyl, hydroxyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, ureido, $-NR^aR^b$, $-SO_2NR^aR^b$ and a group of the formula $-CONR^aR^b$ (wherein R^a is hydrogen or (1-6C)alkyl and R^b selected from hydrogen, (1-6C)alkyl, (3-7)cycloalkyl, heteroaryl and wherein any alkyl, (3-7)cycloalkyl, heteroaryl in R^a and R^b are optionally substituted by 1 or 2 substituents selected from hydroxy and (1-4C)alkoxy;

or R^a and R^b together with the nitrogen atom to which they are attached form a azetidin-1-yl, pyrrolin-1-yl, 1,2,3,6-tetrahydropyridin-1-yl, pyrrolidin-1-yl, piperidino, piperazin-1-yl or morpholino ring, which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from hydroxyl and optionally substituted on any available ring nitrogen by a substituent selected from (1-4C)alkyl and (2-4C)alkanoyl (provided the ring is not thereby quaternised),
or, when two R^1 groups are attached to adjacent carbon atoms, they may, together with the carbon atoms to which they are attached, form a pyrrole ring, wherein the pyrrole ring is optionally substituted by 1 or 2 substituents independently selected from hydroxy;
or, when two R^1 groups are attached to adjacent carbon atoms, they may, together form a (1-3C)alkylenedioxy group.

(d) m is 0, 1 or 2 and R^1 is independently selected from fluoro, chloro, methoxy, methyl, hydroxyl, methylthio, isobutylthio, sulfamoyl, and a group of the formula $-CONR^aR^b$ (wherein R^a is hydrogen or methyl and R^b selected from hydrogen, methyl, ethyl, isobutyl, furanyl, cyclopentyl and cyclohexyl, wherein any alkyl, (3-7)cycloalkyl, heteroaryl in R^a and R^b are optionally substituted by 1 or 2 substituents selected from hydroxy and methoxy;

or R^a and R^b together with the nitrogen atom to which they are attached form a 1,2,3,6-tetrahydropyridin-1-yl, pyrrolidin-1-yl, piperidino, piperazin-1-yl or morpholino ring, which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from hydroxyl and optionally substituted on any available ring nitrogen by a substituent selected from methyl and acetyl (provided the ring is not thereby quaternised), or, when two R^1 groups are attached to adjacent carbon atoms, they may, together with the carbon atoms to which they are attached, form a pyrrole ring, wherein the pyrrole ring is optionally substituted by 1 or 2 substituents independently selected from hydroxy;
or, when two R^1 groups are attached to adjacent carbon atoms, they may, together form a (1-3C)alkylenedioxy group.

(e) m is 0, 1 or 2 and R^1 is independently selected from fluoro, chloro, cyano, trifluoromethyl, methyl, methoxy, methylthio, isobutylthio, sulfamoyl, and a group of the formula $-CONR^aR^b$ (wherein R^a is hydrogen or methyl and R^b selected from hydrogen, methyl, ethyl, isobutyl, furanyl, cyclopentyl and cyclohexyl, wherein any alkyl, (3-7)cycloalkyl, heteroaryl in R^a and R^b are optionally substituted by 1 or 2 substituents selected from hydroxy and methoxy;

or R^a and R^b together with the nitrogen atom to which they are attached form a 1,2,3,6-tetrahydropyridin-1-yl, pyrrolidin-1-yl, piperidino, piperazin-1-yl or morpholino ring, which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from hydroxyl and optionally substituted on any available ring nitrogen by a substituent selected from methyl and acetyl (provided the ring is not thereby quaternised), or, when two R^1 groups are attached to adjacent carbon atoms, they may, together with the carbon atoms to which they are attached, form a pyrrole ring, wherein the pyrrole ring is optionally substituted by 1 or 2 substituents independently selected from hydroxy;
or, when two R^1 groups are attached to adjacent carbon atoms, they may, together form a (1-3C)alkylenedioxy group.

(f) m is 2 and R^1 is positioned in the 2- and 3-position of ring A and R^1 is independently selected from fluoro and chloro.

2. Definitions of A

(a) A is phenyl or pyrid-3-yl.

(b) A is phenyl.

3. Definitions of R^2

(a) R^2 is selected from hydrogen, (1-6C)alkyl and a group of the formulal R^7O-, wherein R^7 is (1-6C)alkyl optionally substituted by 1 or 2 substituents independently selected from hydroxy and a group of the formula R^8O- (wherein R^8 is (1-3C)alkyl).

(b) R^2 is selected from hydrogen, methyl, ethyl and a group of the formulal R^7O-, wherein R^7 is methyl or ethyl.

(c) R^2 is methoxy.

(d) R^2 is hydrogen.

4. Position of R^2 on the quinazoline ring

(a) R^2 is in the 6-position and the substituted-pyrrolidinyloxy group is in the 7-position of the quinazoline ring.

(b) R^2 is in the 7-position and the substituted-pyrrolidinyloxy group is in the 6-position of the quinazoline ring.

5. Definitions of R^3

(a) R^3 is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-3C)alkyl (2-6C)alkanoyl;

and wherein any (1-6C)alkyl or (2-6C)alkanoyl group within R^3 is optionally substituted by 1or 2 substituents independently selected from halogeno, hydroxy and (1-6C)alkyl and/or optionally a substituent selected from cyano, nitro, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy and NR^cR^d, wherein R^c is hydrogen or (1-4C)alkyl and R^d is hydrogen or (1-4C)alkyl.

(b) R^3 is selected from hydrogen, (1-6C)alkyl and (2-6C)alkanoyl;

and wherein any (1-6C)alkyl or (2-6C)alkanoyl group within R^3 is optionally substituted by 1or 2 substituents independently selected from halogeno, hydroxy and (1-4C)alkyl and/or optionally a substituent selected from cyano, nitro, (1-4C)alkoxy and NR^cR^d, wherein R^c is hydrogen or (1-4C)alkyl and R^d is hydrogen or (1-4C)alkyl.

(c) R^3 is selected from hydrogen, methyl, ethyl, acetyl and propionyl;

and wherein any (1-6C)alkyl or (2-6C)alkanoyl group within R^3 is optionally substituted by 1substituent independently selected from NR^cR^d, wherein R^c is hydrogen or methyl and R^d is hydrogen or methyl.

(d) R^3 is hydrogen or methyl.

(e) R^3 is methyl.

6. Definitions of n and R^4

(a) n is 0, 1 or 2 and R^4 is independently selected from methyl, ethyl, methoxy, ethoxy, hydroxyl and oxo.

(b) n is 0 or 1 and R^4 is independently selected from methyl, ethyl, methoxy, ethoxy, hydroxyl and oxo.

(c) n is 0.

7. Position of the $-CONR^5R^6$ group on the pyrrolidine ring

(a) The $-CONR^5R^6$ group is in the 2-position of the pyrrolidine ring.

8. Position of the substituted-quinazolinyloxy group on the pyrrolidine ring

(a) The substituted-quinazolinyloxy group is in the 3-position or the 4-position of the pyrrolidine ring.

(b) The substituted-quinazolinyloxy group is in the 3-position of the pyrrolidine ring.

9. Defintions of R^5 and R^6

(a) R^5 is hydrogen or (1-6C)alkyl and R^6 is selected from hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (3-7)cycloalkyl, heterocyclyl, heteroaryl, (3-7)cycloalkyl(1-3C)alkyl, (3-7)heterocyclyl(1-3C)alkyl and heteroaryl(1-3C)alkyl, and wherein any (1-3C)alkyl, (1-6C)alkyl, (3-7)cycloalkyl, heteroaryl or heterocyclyl group within R^5 or R^6 is optionally substituted (on any available carbon atoms) by 1or 2 substituents independently selected from halogeno, hydroxy(1-6C)alkyl, (1-6C)alkoxycarbonyl,

carbamoyl, (2-6C)alkanoylamino and hydroxy and/or optionally a substituent selected from oxo, cyano and (1-4C)alkoxy,

and wherein any heterocyclyl group within R^6 is optionally substituted on any available ring nitrogen (provided the ring is not thereby quaternised) by (1-4C)alkyl or (2-4C)alkanoyl, or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4, 5 or 6 membered ring which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from halogeno, hydroxy, (1-4C)alkyl and (1-3C)alkylenedioxy, and optionally substituted on any available ring nitrogen by a substituent selected from (1-4C)alkyl and (2-4C)alkanoyl (provided the ring is not thereby quaternised),

and wherein any (1-4C)alkyl or (2-4C)alkanoyl group present as a substituent on the ring formed by R^5 and R^6 together with the nitrogen atom to which they are attached is optionally substituted by 1or 2 substituents independently selected from halogeno and hydroxy and/or optionally a substituent selected from (1-4C)alkyl and (1-4C)alkoxy;

provided that when the pyrrolidinyloxy group is linked to the 6-position of the quinazoline ring, m is 2 and substituents R^1 are both halogeno and attached to the 2- and 3- positions of the ring A, then R^6 is selected from substituted-(1-6C)alkyl (wherein substituted-(1-6C)alkyl is (1-6C)alkyl substituted by 1 or 2 substituents independently selected from halogeno, hydroxy(1-6C)alkyl, (1-6C)alkoxycarbonyl, carbamoyl, (2-6C)alkanoylamino and hydroxy and/or optionally a substituent selected from oxo, cyano and (1-4C)alkoxy), (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (3-7)cycloalkyl, (C1-6)alkylsulfonyl, (3-7)heterocyclyl, heteroaryl, (3-7)cycloalkyl(1-6C)alkyl, (3-7)heterocyclyl(1-6C)alkyl and heteroaryl(1-6C)alkyl,

and wherein any (3-7)cycloalkyl, heteroaryl or (3-7)heterocyclyl group within R^5 or R^6 is optionally substituted (on any available carbon atoms) by 1 or 2 substituents independently selected from halogeno, hydroxy(1-6C)alkyl, (1-6C)alkoxycarbonyl, carbamoyl, (2-6C)alkanoylamino and hydroxy and/or optionally a substituent selected from oxo, cyano, nitro and (1-4C)alkoxy,

and wherein any heterocyclyl group within R^6 is optionally substituted on any available ring nitrogen (provided the ring is not thereby quaternised) by (1-4C)alkyl or (2-4C)alkanoyl, or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4, 5 or 6 membered ring which is substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from (1-3C)alkylenedioxy.

(b) R^5 is hydrogen, methyl, ethyl propyl, isopropyl or isobutyl and R^6 is selected from hydrogen, methyl, ethyl propyl, isopropyl, isobutyl, vinyl, isopropenyl, allyl, but-2-enyl ethynyl, 2-propynyl, butynyl, methoxy, ethoxy propoxy,isopropoxy, cyclopropyl, cyclopentyl, cyclohexyl, azetidinyl, oxazepanyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl; piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, tetrahydrothienyl, tetrahydrothiopyranyl, thiomorpholinyl, pyrazolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidyl, furanyl, pyrazolyl, thiazolyl, isothiazolyl, thiadiazolyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, azetidinylmethyl, oxazepanylmethyl, pyrrolinylmethyl, pyrrolidinylmethyl, morpholinylmethyl, tetrahydro-1,4-thiazinylmethyl, piperidinylmethyl, homopiperidinylmethyl, piperazinylmethyl, homopiperazinylmethyl, dihydropyridinylmethyl, tetrahydropyridinylmethyl, dihydropyrimidinylmethyl, tetrahydropyrimidinylmethyl, tetrahydrothienylmethyl, tetrahydrothiopyranylmethyl, thiomorpholinylmethyl, pyrazolylmethyl, thienylmethyl, oxazolylmethyl, isoxazolylmethyl, imidazolylmethyl, pyridinylmethyl, pyridazinylmethyl, pyrazinylmethyl, pyrimidylmethyl, furanylmethyl, pyrazolylmethyl, thiazolylmethyl, isothiazolylmethyl, thiadiazolylmethyl, 2-(azetidinyl)ethyl, 2-(oxazepanyl)ethyl, 2-(pyrrolinyl)ethyl, 2-(pyrrolidinyl)ethyl, 2-(morpholinyl)ethyl, 2-(tetrahydro-1,4-thiazinyl)ethyl, 2-(piperidinyl)ethyl, 2-(homopiperidinyl)ethyl, 2-(piperazinyl)ethyl, 2-(homopiperazinyl)ethyl, 2-(dihydropyridinyl)ethyl, 2-(tetrahydropyridinyl)ethyl, 2-(dihydropyrimidinyl)ethyl, 2-(tetrahydropyrimidinyl)ethyl, 2-(tetrahydrothienyl)ethyl, 2-(tetrahydrothiopyranyl)ethyl, 2-(thiomorpholinyl)ethyl, 2-(pyrazolyl)ethyl, 2-(thienyl)ethyl, 2-(oxazolyl)ethyl, 2-(isoxazolyl)ethyl, 2-(imidazolyl)ethyl, 2-(pyridinyl)ethyl, 2-(pyridazinyl)ethyl, 2-(pyrazinyl)ethyl, 2-(pyrimidyl)ethyl, 2-(furanyl)ethyl, 2-(pyrazolyl)ethyl, 2-(thiazolyl)ethyl, 2-(isothiazolyl)ethyl and 2-(thiadiazolyl)ethyl,

and wherein any alkyl, cycloalkyl, heteroaryl or heterocyclyl group within R^5 or R^6 is optionally substituted (on any available carbon atoms) by 1or 2 substituents independently selected from fluoro, chloro, bromo, hydroxymethyl, 2-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, carbamoyl, acetamido, propionamido and hydroxy and/or optionally a substituent selected from oxo, cyano, methoxy and ethoxy,

and wherein any heterocyclyl group within R^6 is optionally substituted on any available ring nitrogen (provided the ring is not thereby quaternised) by methyl, ethyl, acetyl or propionyl, or

R^5 and R^6 together with the nitrogen atom to which they are attached form a azetidin-1-yl, pyrrolin-1-yl, pyrrolidin-1-yl, piperidino, morpholino or piperazino ring which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from fluoro, chloro, bromo, hydroxy, methyl, ethyl and propylenedioxy, and optionally substituted on any available ring nitrogen by a substituent selected from methyl, ethyl, acetyl and propionyl (provided the ring is not thereby quaternised),

and wherein any alkyl or alkanoyl group present as a substituent on the ring formed by R^5 and R^6 together with the nitrogen atom to which they are attached is optionally substituted by 1or 2 substituents independently selected from fluoro, chloro, bromo and hydroxy and/or optionally a substituent selected from methyl, ethyl, methoxy and ethoxy;

provided that when the pyrrolidinyloxy group is linked to the 6-position of the quinazoline ring, m is 2 and substituents R^1 are both halogeno and attached to the 2- and 3- positions of the ring A, then R^6 is selected from substituted-methyl, substituted-ethyl substituted-propyl, substituted-isopropyl, substituted-isobutyl, (wherein the substituted groups are substituted by 1 or 2 substituents independently selected from fluoro, chloro, bromo, hydroxymethyl, 2-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, carbamoyl, acetamido, propionamido and hydroxy and/or optionally a substituent selected from oxo, cyano, methoxy and ethoxy) vinyl, isopropenyl, allyl, but-2-enyl ethynyl, 2-propynyl, butynyl, methoxy, ethoxy propoxy,isopropoxy, cyclopropyl, cyclopentyl, cyclohexyl, azetidinyl, oxazepanyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, tetrahydrothienyl, tetrahydrothiopyranyl, thiomorpholinyl, pyrazolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidyl, furanyl, pyrazolyl, thiazolyl, isothiazolyl, thiadiazolyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, azetidinylmethyl, oxazepanylmethyl, pyrrolinylmethyl, pyrrolidinylmethyl, morpholinylmethyl, tetrahydro-1,4-thiazinylmethyl, piperidinylmethyl, homopiperidinylmethyl, piperazinylmethyl, homopiperazinylmethyl, dihydropyridinylmethyl, tetrahydropyridinylmethyl, dihydropyrimidinylmethyl, tetrahydropyrimidinylmethyl, tetrahydrothienylmethyl, tetrahydrothiopyranylmethyl, thiomorpholinylmethyl, pyrazolylmethyl, thienylmethyl, oxazolylmethyl, isoxazolylmethyl, imidazolylmethyl, pyridinylmethyl, pyridazinylmethyl, pyrazinylmethyl, pyrimidylmethyl, furanylmethyl, pyrazolylmethyl, thiazolylmethyl, isothiazolylmethyl, thiadiazolylmethyl, 2-(azetidinyl)ethyl,

2-(oxazepanyl)ethyl, 2-(pyrrolinyl)ethyl, 2-(pyrrolidinyl)ethyl, 2-(morpholinyl)ethyl, 2-(tetrahydro-1,4-thiazinyl)ethyl, 2-(piperidinyl)ethyl, 2-(homopiperidinyl)ethyl, 2-(piperazinyl)ethyl, 2-(homopiperazinyl)ethyl, 2-(dihydropyridinyl)ethyl, 2-(tetrahydropyridinyl)ethyl, 2-(dihydropyrimidinyl)ethyl, 2-(tetrahydropyrimidinyl)ethyl, 2-(tetrahydrothienyl)ethyl, 2-(tetrahydrothiopyranyl)ethyl, 2-(thiomorpholinyl)ethyl, 2-(pyrazolyl)ethyl, 2-(thienyl)ethyl, 2-(oxazolyl)ethyl, 2-(isoxazolyl)ethyl, 2-(imidazolyl)ethyl, 2-(pyridinyl)ethyl, 2-(pyridazinyl)ethyl, 2-(pyrazinyl)ethyl, 2-(pyrimidyl)ethyl, 2-(furanyl)ethyl, 2-(pyrazolyl)ethyl, 2-(thiazolyl)ethyl, 2-(isothiazolyl)ethyl and 2-(thiadiazolyl)ethyl,

and wherein any cycloalkyl, heteroaryl or heterocyclyl group within R^5 or R^6 is optionally substituted (on any available carbon atoms) by 1or 2 substituents independently selected from fluoro, chloro, bromo, hydroxymethyl, 2-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, carbamoyl, acetamido, propionamido and hydroxy and/or optionally a substituent selected from oxo, cyano, methoxy and ethoxy,

and wherein any heterocyclyl group within R^6 is optionally substituted on any available ring nitrogen (provided the ring is not thereby quaternised) by methyl, ethyl, acetyl or propionyl, or

R^5 and R^6 together with the nitrogen atom to which they are attached form a azetidin-1-yl, pyrrolin-1-yl, pyrrolidin-1-yl, piperidino, morpholino or piperazino ring which is substituted on adjacent ring carbon atoms by a propylenedioxy group, and optionally substituted on any available ring nitrogen by a substituent selected from methyl, ethyl, acetyl and propionyl (provided the ring is not thereby quaternised).

(c) R^5 is hydrogen, methyl or ethyl and R^6 is selected from hydrogen, methyl, ethyl propyl, isopropyl, isobutyl, vinyl, isoprop-2-enyl, allyl, but-2-enyl ethynyl, 2-prop-2-ynyl, but-3-ynyl, methoxy, ethoxy, cyclopropyl, cyclopentyl, cyclohexyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrahydropyridinyl, thiomorpholinyl, 1,2,3,6-tetrahydropyridin-1-yl, pyrazolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidyl, furanyl, pyrazolyl, thiazolyl, isothiazolyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, azetidinylmethyl, pyrrolinylmethyl, pyrrolidinylmethyl, morpholinylmethyl, piperidinylmethyl, piperazinylmethyl, tetrahydropyridinylmethyl, thiomorpholinylmethyl, pyrazolylmethyl, thienylmethyl, oxazolylmethyl, isoxazolylmethyl, imidazolylmethyl, pyridinylmethyl, pyridazinylmethyl, pyrazinylmethyl, pyrimidylmethyl,

furanylmethyl, pyrazolylmethyl, thiazolylmethyl, isothiazolylmethyl, 2-(azetidinyl)ethyl2-(pyrrolinyl)ethyl, 2-(pyrrolidinyl)ethyl, 2-(morpholinyl)ethyl, 2-(piperidinyl)ethyl, 2-(piperazinyl)ethyl, 2-(tetrahydropyridinyl)ethyl, 2-(thiomorpholinyl)ethyl, 2-(pyrazolyl)ethyl, 2-(thienyl)ethyl, 2-(oxazolyl)ethyl, 2-(isoxazolyl)ethyl, 2-(imidazolyl)ethyl, 2-(pyridinyl)ethyl, 2-(pyridazinyl)ethyl, 2-(pyrazinyl)ethyl, 2-(pyrimidyl)ethyl, 2-(furanyl)ethyl, 2-(pyrazolyl)ethyl, 2-(thiazolyl)ethyl and 2-(isothiazolyl)ethyl,

and wherein any alkyl, cycloalkyl, heteroaryl or heterocyclyl group within R^5 or R^6 is optionally substituted (on any available carbon atoms) by 1or 2 substituents independently selected from fluoro, chloro, bromo, hydroxymethyl, 2-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, carbamoyl, acetamido and hydroxy and/or optionally a substituent selected from oxo, cyano, methoxy and ethoxy,

and wherein any heterocyclyl group within R^6 is optionally substituted on any available ring nitrogen (provided the ring is not thereby quaternised) by methyl, ethyl, acetyl or propionyl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a azetidin-1-yl, pyrrolin-1-yl, pyrrolidin-1-yl, piperidino, morpholino or piperazino ring which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from fluoro, chloro, hydroxy, methyl, ethyl and propylenedioxy, and optionally substituted on any available ring nitrogen by a substituent selected from methyl, ethyl, acetyl and propionyl (provided the ring is not thereby quaternised),

and wherein any alkyl or alkanoyl group present as a substituent on the ring formed by R^5 and R^6 together with the nitrogen atom to which they are attached is optionally substituted by 1or 2 substituents independently selected from fluoro, chloro and hydroxy and/or optionally a substituent selected from methyl, ethyl, methoxy and ethoxy;

provided that when the pyrrolidinyloxy group is linked to the 6-position of the quinazoline ring, m is 2 and substituents R^1 are both halogeno and attached to the 2- and 3-positions of the ring A, then R^6 is selected from substituted-methyl, substituted-ethyl substituted-propyl, substituted-isopropyl, substituted-isobutyl, (wherein the substituted groups are substituted by 1 or 2 substituents independently selected from fluoro, chloro, bromo, hydroxymethyl, 2-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, carbamoyl, acetamido and hydroxy and/or optionally a substituent selected from oxo, cyano, methoxy and ethoxy), vinyl, isoprop-2-enyl, allyl, but-2-enyl ethynyl, 2-prop-2-ynyl, but-3-ynyl, methoxy, ethoxy, cyclopropyl, cyclopentyl, cyclohexyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrahydropyridinyl, thiomorpholinyl, 1,2,3,6-tetrahydropyridin-1-yl,

pyrazolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidyl, furanyl, pyrazolyl, thiazolyl, isothiazolyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, azetidinylmethyl, pyrrolinylmethyl, pyrrolidinylmethyl, morpholinylmethyl, piperidinylmethyl, piperazinylmethyl, tetrahydropyridinylmethyl, thiomorpholinylmethyl, pyrazolylmethyl, thienylmethyl, oxazolylmethyl, isoxazolylmethyl, imidazolylmethyl, pyridinylmethyl, pyridazinylmethyl, pyrazinylmethyl, pyrimidylmethyl, furanylmethyl, pyrazolylmethyl, thiazolylmethyl, isothiazolylmethyl, 2-(azetidinyl)ethyl2-(pyrrolinyl)ethyl, 2-(pyrrolidinyl)ethyl, 2-(morpholinyl)ethyl, 2-(piperidinyl)ethyl, 2-(piperazinyl)ethyl, 2-(tetrahydropyridinyl)ethyl, 2-(thiomorpholinyl)ethyl, 2-(pyrazolyl)ethyl, 2-(thienyl)ethyl, 2-(oxazolyl)ethyl, 2-(isoxazolyl)ethyl, 2-(imidazolyl)ethyl, 2-(pyridinyl)ethyl, 2-(pyridazinyl)ethyl, 2-(pyrazinyl)ethyl, 2-(pyrimidyl)ethyl, 2-(furanyl)ethyl, 2-(pyrazolyl)ethyl, 2-(thiazolyl)ethyl and 2-(isothiazolyl)ethyl,

and wherein any cycloalkyl, heteroaryl or heterocyclyl group within R^5 or R^6 is optionally substituted (on any available carbon atoms) by 1or 2 substituents independently selected from fluoro, chloro, bromo, hydroxymethyl, 2-hydroxyethyl, methoxycarbonyl, ethoxycarbonyl, carbamoyl, acetamido and hydroxy and/or optionally a substituent selected from oxo, cyano, methoxy and ethoxy,

and wherein any heterocyclyl group within R^6 is optionally substituted on any available ring nitrogen (provided the ring is not thereby quaternised) by methyl, ethyl, acetyl or propionyl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a azetidin-1-yl, pyrrolin-1-yl, pyrrolidin-1-yl, piperidino, morpholino or piperazino ring which is substituted on adjacent ring carbon atoms by a propylenedioxy group, and optionally substituted on any available ring nitrogen by a substituent selected from methyl, ethyl, acetyl and propionyl (provided the ring is not thereby quaternised).

(d) R^5 is hydrogen or methyl and R^6 is selected from hydrogen, methyl, ethyl, propyl, isopropyl, vinyl, isoprop-2-enyl, allyl, but-2-enyl ethynyl, 2-propynyl, but-3-ynyl, methoxy, cyclopropyl, cyclopentyl, 1-(hydroxymethyl)cyclopentyl, cyclohexyl, 4-hydroxycyclohexyl, cyclopropylmethyl, cyclopentylmethyl, methoxymethyl, 2-(methoxy)ethyl, 2-(ethoxy)ethyl, carbamoylmethyl, 2-(acetyl)ethyl, cyanomethyl, 2-(cyano)ethyl, 2,3-dihydroxypropyl, 2-(hydroxyl)-1,1-dimethylethyl, 2,2,2-trifluoroethyl, 1-(ethoxycarbonyl)-2-hydroxyethyl, 2-acetamido)ethyl, tetrahydrofuran-2-ylmethyl, imidazol-2-ylmethyl, 1-methylpyrazol-5-yl, 1-

methylpyrazol-5-yl, 3-methylpyrazol-5-yl, imidazol-1-ylmethyl, 2-(imidazol-1-yl)ethyl, furan-2-ylmethyl, 2-(furan-2-yl)ethyl, 5-methylisoxazol-3-ylmethyl, thien-3yl, morpholino, piperidin-4-yl, 1-methylpiperidin-4-yl, tetrahydro-2H-pyran-4-yl and 3-oxotetrahydrofuran-4-yl,

or R^5 and R^6 together with the nitrogen atom to which they are attached form a 3-hydroxyazetidin-1-yl, 2-carbamoylazetidin-1-yl, pyrrolin-1-yl, pyrrolidin-1-yl, 3-hydroxy, pyrrolidin-1-yl, piperidino, morpholino or piperazino group;

provided that when the pyrrolidinyloxy group is linked to the 6-position of the quinazoline ring, m is 2 and substituents R^1 are both halogeno and attached to the 2- and 3-positions of the ring A, then R^6 is selected from vinyl, isoprop-2-enyl, allyl, but-2-enyl ethynyl, 2-propynyl, but-3-ynyl, methoxy, cyclopropyl, cyclopentyl, 1-(hydroxymethyl)cyclopentyl, cyclohexyl, 4-hydroxycyclohexyl, cyclopropylmethyl, cyclopentylmethyl, methoxymethyl, 2-(methoxy)ethyl, 2-(ethoxy)ethyl, carbamoylmethyl, 2-(acetyl)ethyl, cyanomethyl, 2-(cyano)ethyl, 2,3-dihydroxypropyl, 2-(hydroxyl)-1,1-dimethylethyl, 2,2,2-trifluoroethyl, 1-(ethoxycarbonyl)-2-hydroxyethyl, 2-acetamido)ethyl, tetrahydrofuran-2-ylmethyl, imidazol-2-ylmethyl, 1-methylpyrazol-5-yl, 1-methylpyrazol-5-yl, 3-methylpyrazol-5-yl, imidazol-1-ylmethyl, 2-(imidazol-1-yl)ethyl, furan-2-ylmethyl, 2-(furan-2-yl)ethyl, 5-methylisoxazol-3-ylmethyl, thien-3yl, morpholino, piperidin-4-yl, 1-methylpiperidin-4-yl, tetrahydro-2H-pyran-4-yl and 3-oxotetrahydrofuran-4-yl.

Particular classes of compounds are disclosed in Table A using combinations of the definitions described hereinabove. For example, 'a' in the column headed R^2 in the table refers to definition (a) given for R^2 hereinabove.

Table A

Class	n and R^1	A	R^2	Position of R^2	R^3	n and R^4	Position of -CONR^{5}R^6	Position of quinazolinyloxy	R^5 and R^6
1	a	a	I	I	I	a	I	I	I
2	a	a	a	I	a	a	a	a	I
3	b	b	a	I	a	a	a	a	a
4	c	b	a	I	b	b	a	b	a
5	d	b	b	b	b	c	a	b	b
6	e	b	b	b	c	c	a	b	c
7	f	b	d	a	d	c	a	b	I
8	f	b	b	b	d	c	a	b	c
9	f	b	c	b	d	c	a	b	d
10	f	b	c	b	e	c	a	b	d

Particular compounds of the present invention include:

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-*N*,*N*,1-trimethyl-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-1-methyl-L-prolinamide trifluoroacetic acid salt;

(4*S*)-4-({4-[(4-cyano-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-4-cyanophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-[(4-{[3-chloro-4-(trifluoromethyl)phenyl]amino}-7-methoxyquinazolin-6-yl)oxy]-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(5-chloropyridin-3-yl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(2-fluoro-4-methylphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-4-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(2-fluoro-4-hydroxyphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(2,4-difluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(2,5-difluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(5-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(4-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(5-chloro-2-hydroxyphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-4-methoxyphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-[(4-{[2-(aminosulfonyl)-5-chlorophenyl]amino}-7-methoxyquinazolin-6-yl)oxy]-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({7-methoxy-4-[(2,3,4-trifluorophenyl)amino]quinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-[(4-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-7-methoxyquinazolin-6-yl)oxy]-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-[(4-{[2-fluoro-3-(trifluoromethyl)phenyl]amino}-7-methoxyquinazolin-6-yl)oxy]-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-methoxyphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-methylphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-4-hydroxyphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(3-ethynylphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-{[4-(1*H*-indol-5-ylamino)-7-methoxyquinazolin-6-yl]oxy}-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-1*H*-indol-5-yl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-cyclopropyl-1-methyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-(cyclopropylmethyl)-1-methyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-(2-methoxyethyl)-1-methyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-cyclopentyl-1-methyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-(2-methoxyethyl)-*N*,1-dimethyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-methoxy-1-methyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-cyclohexyl-1-methyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-D-prolinamide; and

(4*S*)-4-({4-[(3-chloro-4-fluorophenyl)amino]-6-methoxyquinazolin-7-yl}oxy)-*N*,*N*,1-trimethyl-L-prolinamide;

and pharmaceutically-acceptable salts thereof.

Further particular compounds of the present invention include:

(4*S*)-4-({4-[(3-chloro-4-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*-dimethyl-L-prolinamide;

(4*S*)-4-({4-[(5-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*-dimethyl-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2,4-difluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*-dimethyl-L-prolinamide;

(4*S*)-4-({4-[(5-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2,4-difluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-4-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-L-prolinamide;

(4*S*)-4-{[4-(1*H*-indol-5-ylamino)-7-methoxyquinazolin-6-yl]oxy}-*N*,*N*-dimethyl-L-prolinamide;

(4*S*)-4-{[4-(1*H*-indol-5-ylamino)-7-methoxyquinazolin-6-yl]oxy}-*N*,*N*,1-trimethyl-L-prolinamide;

(4*S*)-4-{[4-(1,3-benzodioxol-4-ylamino)-7-methoxyquinazolin-6-yl]oxy}-*N*,*N*,1-trimethyl-L-prolinamide;

(4*S*)-4-[(4-{[5-(aminocarbonyl)-3-chloro-2-fluorophenyl]amino}-7-methoxyquinazolin-6-yl)oxy]-*N*,*N*,1-trimethyl-L-prolinamide;

(4*R*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-cyclohexyl-1-methyl-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-cyclopropyl-1-methyl-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-(2-methoxyethyl)-1-methyl-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-cyclohexyl-*N*,1-dimethyl-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-(2-methoxyethyl)-*N*,1-dimethyl-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,1-dimethyl-*N*-(1-methylpiperidin-4-yl)-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-cyclopentyl-1-methyl-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-methoxy-1-methyl-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-(cyclopropylmethyl)-1-methyl-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-cyclohexyl-1-methyl-L-prolinamide;

(4*R*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-*N*-prop-2-yn-1-yl-L-prolinamide;

(4*R*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-(2-methoxyethyl)-1-methyl-L-prolinamide;

(4*R*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-cyclopropyl-1-methyl-L-prolinamide;

(4*R*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-cyclopentyl-1-methyl-L-prolinamide;

1-[[(2*S*,4*R*)-4-[[4-[(3-chloro-2-fluorophenyl)amino]-7-methoxy-6-quinazolinyl]oxy]-1-methyl-2-pyrrolidinyl]carbonyl]-3-pyrroline;

(4*R*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-(cyclopropylmethyl)-1-methyl-L-prolinamide;

(4*R*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-cyclohexyl-*N*,1-dimethyl-L-prolinamide;

(4*R*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-(2-cyanoethyl)-1-methyl-L-prolinamide;

(4*R*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-(cyanomethyl)-1-methyl-L-prolinamide;

(4*R*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-(cyanomethyl)-*N*,1-dimethyl-L-prolinamide;

(4*R*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)-L-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-[(1*R*)-1-(hydroxymethyl)-3-methylbutyl]-1-methyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-(3-furylmethyl)-1-methyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-*N*-[(5-methylisoxazol-3-yl)methyl]-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-[2-(1*H*-imidazol-1-yl)ethyl]-1-methyl-D-prolinamide;

(2*S*)-1-[(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-D-prolyl]azetidine-2-carboxamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-[(2*R*)-2,3-dihydroxypropyl]-1-methyl-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-*N*-(1-methyl-1*H*-pyrazol-5-yl)-D-prolinamide;

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-*N*-3-thienyl-D-prolinamide; and

(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-*N*-(3-methyl-1*H*-pyrazol-5-yl)-D-prolinamide;

and pharmaceutically-acceptable salts thereof.

Synthesis of Quinazoline Derivatives of the Formula I

A further aspect the present invention provides a process for preparing a quinazoline derivative of Formula I or a pharmaceutically-acceptable salt thereof. It will be appreciated that during certain of the following processes certain substituents may require protection to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed.

For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid

as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium, sodium hydroxide or ammonia. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

Resins may also be used as a protecting group.

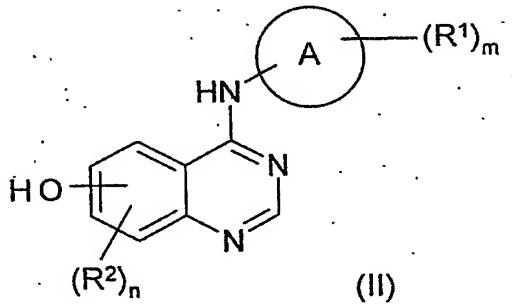
The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention and are illustrated by the following representative examples. Necessary starting materials may be obtained by standard procedures of organic chemistry (see, for example, Advanced Organic Chemistry (Wiley-Interscience), Jerry March). The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively, necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist. Information on

the preparation of necessary starting materials or related compounds (which may be adapted to form necessary starting materials) may also be found in the following Patent and Application Publications, the contents of the relevant process sections of which are hereby incorporated herein by reference: WO94/27965, WO 95/03283, WO 96/33977, WO 96/33978, WO 96/33979, WO 96/33980, WO 96/33981, WO 97/30034, WO 97/38994, WO01/66099, US 5,252,586, EP 520 722, EP 566 226, EP 602 851 and EP 635 507.

The present invention also provides that quinazoline derivatives of the Formula I, or pharmaceutically acceptable salts thereof, can be prepared by a process **(a)** to **(j)** as follows (wherein the variables are as defined above unless otherwise stated) :

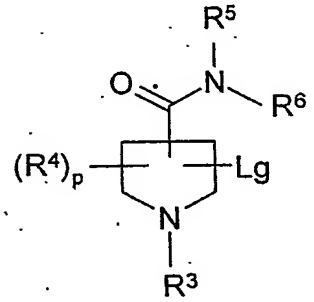
Process (a) By reacting a compound of the Formula II:



(II)

wherein R^1, R^2, A, M and N have any of the meanings defined hereinbefore except that any functional group is protected if necessary,

with a compound of the Formula III:



(III)

wherein R^3, R^4, R^5, R^6 and p have any of the meanings defined hereinbefore except that any functional group is protected if necessary and Lg is a displaceable group, wherein the reaction is conveniently performed in the presence of a suitable base,

and whereafter any protecting group that is present is removed by conventional means.

A convenient displaceable group Lg is, for example, a halogeno, alkanesulfonyloxy or arylsulfonyloxy group, for example a chloro, bromo, methanesulfonyloxy, 4-nitrobenzenesulfonyloxy or toluene-4-sulfonyloxy group (suitably a methanesulfonyloxy, 4-nitrobenzenesulfonyloxy or toluene-4-sulfonyloxy group).

The reaction is advantageously carried out in the presence of base. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or for example, an alkali metal or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, cesium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively such a base is, for example, an alkali metal hydride, for example sodium hydride, an alkali metal or alkaline earth metal amide, for example sodium amide or sodium bis(trimethylsilyl)amide, or a sufficiently basic alkali metal halide, for example cesium fluoride or sodium iodide. The reaction is suitably effected in the presence of an inert solvent or diluent, for example an alkanol or ester such as methanol, ethanol, 2-propanol or ethyl acetate, a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene, or (suitably) a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently effected at a temperature in the range, for example, 10 to 150°C (or the boiling point of the solvent), suitably in the range 20 to 90°C.

Process (b) By modifying a substituent in or introducing a substituent into another quinazoline derivative of Formula I or a pharmaceutically acceptable salt thereof, as hereinbefore defined except that any functional group is protected if necessary, and whereafter any protecting group that is present is removed by conventional means.

Methods for converting substituents into other substituents are known in the art. For example an alkylthio group may be oxidised to an alkylsulfinyl or alkylsulfonyl group, a cyano group reduced to an amino group, a nitro group reduced to an amino group, a hydroxy group alkylated to a methoxy group, a bromo group converted to an alkylthio group or an amino group may be acylated to give an alkanoylamino group (for example by reaction with a suitable acid chloride or acid anhydride). In addition, an R^1 group may be halogenated by reacting it with halogenating agent. For example, a compound of the formula (I) wherein R^1 contains an alkyl group of alkylene group may be chlorinated by reacting it with N-

chlorosuccinimide using conditions known in the art. Conveniently, one R^1 group may be converted into another R^1 group as a final step in the preparation of a compound of the Formula I. It is also possible to introduce a substituent onto the pyrrole group as a final step in the preparation of a compound of the Formula I.

Process (c) By removal of a protecting group from a quinazoline derivative of Formula I, or a pharmaceutically acceptable salt thereof.

Suitable methods for removal of protecting groups are well known and are discussed herein.

Suitable protecting groups for an amino group are, for example, any of the protecting groups disclosed hereinbefore for an amino group. Suitable methods for the cleavage of such amino protecting groups are also disclosed hereinbefore. In particular, a suitable protecting group is a lower alkoxycarbonyl group such as a tert-butoxycarbonyl group which may be cleaved under conventional reaction conditions such as under acid-catalysed hydrolysis, for example in the presence of trifluoroacetic acid.

Process (d) By reacting a compound of the Formula II as hereinbefore defined with a compound of the Formula III as defined hereinbefore except Lg is OH under Mitsunobu conditions, and whereafter any protecting group that is present is removed by conventional means.

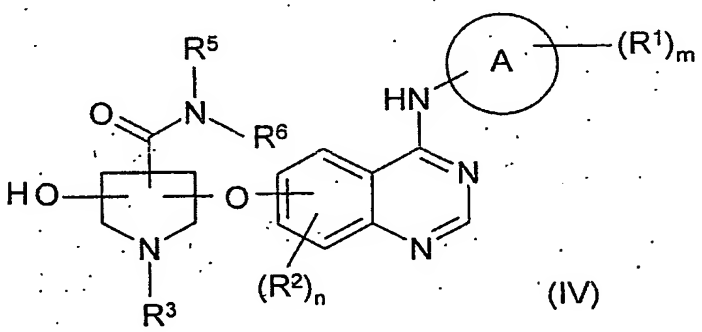
Suitable Mitsunobu conditions include, for example, reaction in the presence of a suitable tertiary phosphine and a di-alkylazodicarboxylate in an organic solvent such as THF, or suitably dichloromethane and in the temperature range 0°C - 60°C, but suitably at ambient temperature. A suitable tertiary phosphine includes for example tri-n-butylphosphine or suitably tri-phenylphosphine. A suitable di-alkylazodicarboxylate includes for example diethyl azodicarboxylate (DEAD) or suitably di-tert-butyl azodicarboxylate. Details of Mitsunobu reactions are contained in Tet. Letts., 31, 699, (1990); The Mitsunobu Reaction, D.L.Hughes, Organic Reactions, 1992, Vol.42, 335-656 and Progress in the Mitsunobu Reaction, D.L.Hughes, Organic Preparations and Procedures International, 1996, Vol.28, 127-164.

Process (e) For the preparation of those compounds of the Formula I wherein R^4 is a hydroxy group by the cleavage of a quinazoline derivative of the Formula I wherein R^4 is a (1-4C)alkoxy group.

The cleavage reaction may conveniently be carried out by any of the many procedures

known for such a transformation. The cleavage reaction of a compound of the Formula I wherein R^4 is a (1-6C)alkoxy group may be carried out, for example, by treatment of the quinazoline derivative with an alkali metal (1-6C)alkylsulfide such as sodium ethanethiolate or, for example, by treatment with an alkali metal diarylphosphide such as lithium diphenylphosphide. Alternatively the cleavage reaction may conveniently be carried out, for example, by treatment of the quinazoline derivative with a boron or aluminium trihalide such as boron tribromide, or by reaction with an organic or inorganic acid, for example trifluoroacetic acid. L-Methionine / methanesulphonic acid is preferredSuch reactions are suitably carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore. A preferred cleavage reaction is the treatment of a quinazoline derivative of the Formula I with pyridine hydrochloride. The cleavage reactions are suitably carried out at a temperature in the range, for example, of from 10 to 150°C, for example from 25 to 80°C.

Process (f) For the preparation of those compounds of the Formula I wherein R^4 is (1-4C)alkoxy, by the reaction of a compound of the Formula IV:



(IV)

with a compound of the formula (1-4C)alkyl-Lg, , wherein Lg is a displaceable group, wherein the reaction is conveniently performed in the presence of a suitable base;

and whereafter any protecting group that is present is removed by conventional means. Suitable displaceable groups, Lg, are as hereinbefore defined for process a, for example chloro or bromo. The reaction is suitably performed in the presence of a suitable base. Suitable solvents, diluents and bases include, for example those hereinbefore described in relation to process (a).

Process (g)

For the preparation of those compounds of the Formula I wherein R^1, R^2, R^4 or R^6 contain a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or

substituted (1-6C)alkylamino group, the alkylation, conveniently in the presence of a suitable base as defined hereinbefore for process a, of a quinazoline derivative of the Formula I wherein R^1, R^2, R^4 or R^6 contain a hydroxy group or a primary or secondary amino group as appropriate. Alkylation may also be used to convert a compound or intermediate wherein R^3 is hydrogen to the corresponding compound wherein R^3 is alkyl or substituted-alkyl.

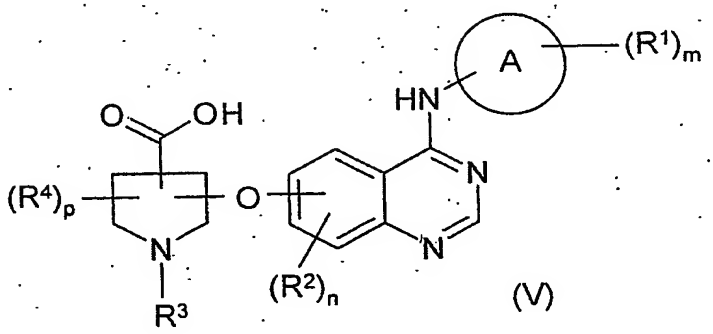
A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to alkoxy or substituted alkoxy, or for the alkylation of amino to alkylamino or substituted alkylamino, for example an alkyl or substituted alkyl halide, for example a (1-6C)alkyl chloride, bromide or iodide or a substituted (1-6C)alkyl chloride, bromide or iodide, conveniently in the presence of a suitable base as defined hereinbefore, in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 140°C, conveniently at or near ambient temperature. An analogous procedure may be used to introduce optionally substituted (2-6C)alkanoyloxy, (2-6C)alkanoylamino and (1-6C)alkanesulfonylamino groups as appropriate.

Conveniently for the production of those compounds of the Formula I wherein R^1 contains a (1-6C)alkylamino or substituted (1-6C)alkylamino group or R^3 is convereted from hydrogen to alkyl or substituted-alkyl, a reductive amination reaction may be employed using formaldehyde or paraformaldehyde, or a (2-6C)alkanolaldehyde (for example acetaldehyde or propionaldehyde). For example, for the production of those compounds of the Formula I wherein R^1 contains an N-methyl group or for the conversion of R^3 from hydrogen to an alkyl or substituted-alkyl group, the corresponding compound containing a N-H group may be reacted with formaldehyde in the presence of a suitable reducing agent. A suitable reducing agent is, for example, a hydride reducing agent, for example formic acid, an alkali metal aluminium hydride such as lithium aluminium hydride, or, suitably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran and diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride and sodium cyanoborohydride. When the reducing agent is formic acid the reaction is conveniently carried out using an aqueous solution of the formic acid. The reaction is

performed at a temperature in the range, for example, 10 to 100°C, such as 70 to 90°C or, conveniently, at or near ambient temperature. Conveniently, when the reducing agent is formic acid, protecting groups such as tert-butoxycarbonyl on the NH group to be alkylated (for example present from the synthesis of the starting material) may be removed in-situ during the reaction.

Process (h)

By reacting a compound of the formula (V) or reactive derivative thereof



(V)

with a compound of the formula HNR^5R^6 or a suitable salt in the presence of a suitable base and in an inert solvent.

The coupling reaction is conveniently carried out in the presence of a suitable coupling agent, such as a carbodiimide, or a suitable peptide coupling agent, for example O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate (HATU) or a carbodiimide such as dicyclohexylcarbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine .

The coupling reaction is conveniently carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, di-isopropylethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate, for example sodium carbonate, potassium carbonate, cesium carbonate or calcium carbonate.

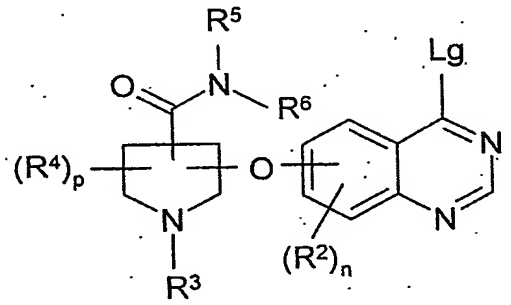
The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an ester such as or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as

N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range, for example, from 0 to 120°C, conveniently at or near ambient temperature.

A "reactive derivative" of the acid of the formula (V) is a carboxylic acid derivative that will react with an amine of formula (III) to give the corresponding amide. A suitable reactive derivative of a carboxylic acid of the formula (V) is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as methanol, ethanol, isopropanol, butanol or N-hydroxybenzotriazole; or an acyl azide, for example an azide formed by the reaction of the acid and azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide. The reaction of such reactive derivatives of carboxylic acid with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature as described above.

Process (i)

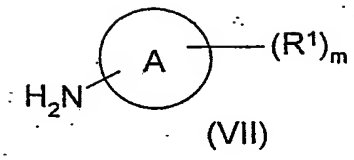
By reacting a compound of the formula VI:



(VI)

wherein R^1, R^2, R^3, R^4, R^5, R^6, n and p, have any of the meanings defined hereinbefore except that any functional group is protected if necessary and Lg is a displaceable group as hereinbefore defined,

with an aniline of the formula VII:



(VII)

wherein R^1 and m have any of the meanings defined hereinbefore except that any functional group is protected if necessary, and wherein the reaction is conveniently performed in the presence of a suitable acid,

and whereafter any protecting group that is present is removed by conventional means.

Suitable displaceable groups represented by Lg are as hereinbefore defined, in particular halogeno such as chloro.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one acetonitrile or dimethylsulfoxide acetonitrile is favoured. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 250°C, conveniently in the range 40 to 120°C or where a solvent or diluent is used at the reflux temperature. Conveniently, the compound of formula VI may is reacted with a compound of the formula VII in the presence of a protic solvent such as isopropanol, conveniently in the presence of an acid, for example hydrogen chloride gas in diethyl ether or dioxane, or hydrochloric acid, for example a 4M solution of hydrogen chloride in dioxane, under the conditions described above. Alternatively, this reaction may be conveniently carried out in an aprotic solvent, such as dioxane or a dipolar aprotic solvent such as N,N-dimethylacetamide or acetonitrile in the presence of an acid, for example hydrogen chloride gas in diethyl ether or dioxane, or hydrochloric acid. The compound of the formula VI, wherein Lg is halogeno, may be reacted with a compound of the formula VII in the absence of an acid. In this reaction displacement of the halogeno leaving group Lg results in the formation of the acid HLg in-situ and auto-catalysis of the reaction. Conveniently the reaction is carried out in a suitable inert organic solvent, for example isopropanol, dioxane or N,N-dimethylacetamide. Suitable conditions for this reaction are as described above.

Alternatively, the compound of formula VI may is reacted with a compound of the formula VII in the presence of a suitable base. Suitable bases for this reaction are as hereinbefore defined under Process (a). This reaction is conveniently performed in an inert solvent or diluent, for example those mentioned above in relation to this process (i);

Process (j)

Forming the group $-CON(R^5)R^6$ by reacting to the corresponding carboxy compound, wherein any functional groups are protected if necessary, with a primary or secondary amine or a hetrocyclic c group containing an NH group; and whereafter any protecting group that is present is removed by conventional means.

The coupling reaction is conveniently carried out in the presence of a suitable coupling agent, such as a carbodiimide (for example1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide), or a suitable peptide coupling agent, for example O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate (HATU). The coupling reaction is conveniently carried out in an inert solvent such as, for example, a halogenated solvent such as methylene chloride, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidinone. Suitably the coupling reaction is carried out in the presence of a suitable base, such as an organic amine, for example di-isopropylethylamine or 4-dimethylaminopyridine. The coupling reaction is suitable performed at -25°C to 150°C, conveniently at ambient temperature.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

When a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid using a conventional procedure. To facilitate isolation of the compound during preparation, the compound may be prepared in the form of a salt that is not a pharmaceutically acceptable salt. The resulting salt can then be modified by conventional techniques to give a pharmaceutically acceptable salt of the compound. Such techniques include, for example ion exchange techniques or re-precipitation of the compound

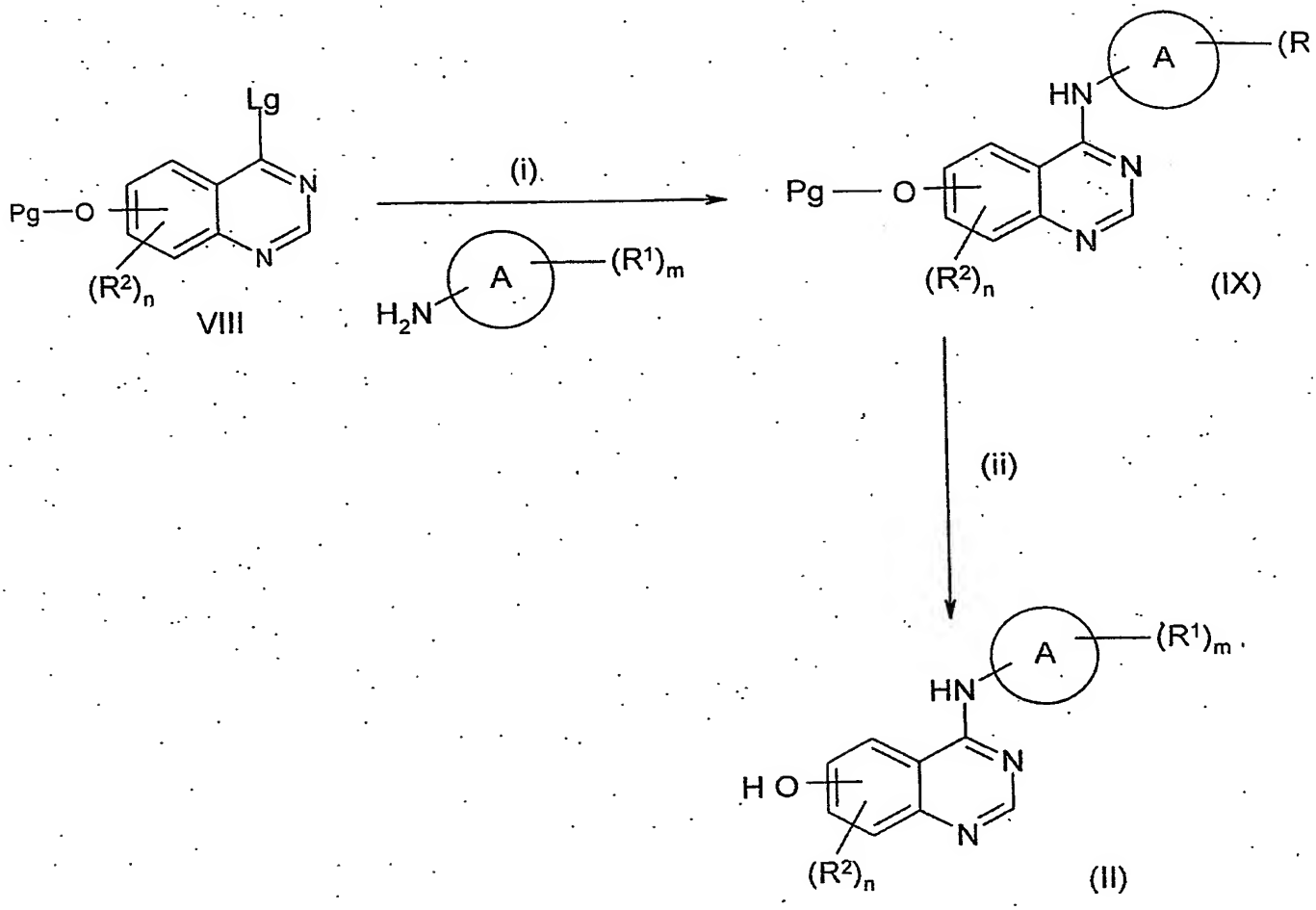
in the presence of a pharmaceutically acceptable counter ion. For example re-precipitation in the presence of a suitable acid such as HCl to give a hydrochloride acid addition salt.

As mentioned hereinbefore some of the compounds according to the present invention may contain one of more chiral centers and may therefore exist as stereoisomers (for example when Q^1 contains a pyrrolidin-3-yl group). Stereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of a racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation by virtue of the different physical properties of the diastereoisomers, for example, by fractional crystallisation, HPLC or flash chromatography. Alternatively particular stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. Examples of suitable chiral synthesis and separation of isomers are described in the Examples. When a specific stereoisomer is isolated it is suitably isolated substantially free for other stereoisomers, for example containing less than 20%, particularly less than 10% and more particularly less than 5% by weight of other stereoisomers.

In the section above the expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Preparation of Starting Materials

Compounds of Formula II are commercially available or may be prepared using conventional techniques or analogous processes to those described in the prior art. In particular those patents and applications listed hereinbefore, such as WO96/15118, WO 01/66099 and EP 566 226. For example, the compounds of Formula II may be prepared in accordance with Reaction Scheme 1:



Reaction Scheme 1

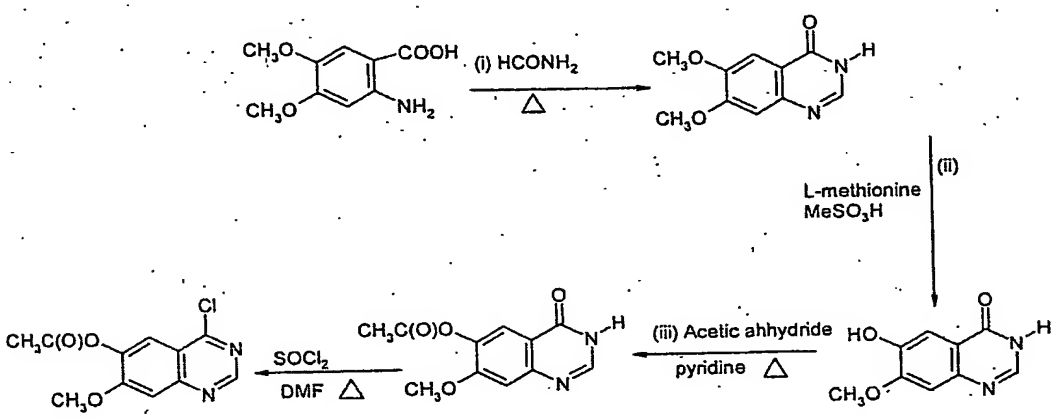
wherein R^1, R^2, m and n are as hereinbefore defined and Pg is a hydroxy protecting group.

(i) Reaction suitably in an inert protic solvent (such as an alkanol for example iso-propanol), an aprotic solvent (such as dioxane) or a dipolar aprotic solvent (such as N,N-dimethylacetamide) in the presence of an acid, for example hydrogen chloride gas in diethyl ether or dioxane, or hydrochloric acid, under analogous conditions to those described above under process (i).

Alternatively the reaction may be carried out in one of the above inert solvents conveniently in the presence of a base, for example potassium carbonate. The above reactions are conveniently carried out at a temperature in the range, for example, 0 to 150°C, suitably at or near the reflux temperature of the reaction solvent.

(ii) Cleavage of Pg may be performed under standard conditions for such reactions. For example when Pg is an alkanoyl group such as acetyl, it may be cleaved by heating in the presence of a methanolic ammonia solution.

Compounds of formula Stat are known or can be prepared using known processes for the preparation of analogous compounds. If not commercially available, compounds of the formula (VIII) may be prepared by procedures which are selected from standard chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the procedures described in the Examples. For example, standard chemical techniques are as described in Houben Weyl. By way of example the compound of the formula VIII in which R^4 is methoxy and in the 7-position of the quinazoline ring, Lg is chloro and Pg is acetyl may be prepared using the process illustrated in Reaction Scheme 2:



Reaction scheme 2

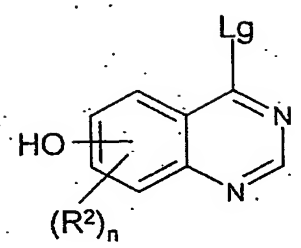
Reaction Scheme 2 may be generalised by the skilled man to apply to compounds within the present specification which are not specifically illustrated (for example to introduce a substituent other than methoxy at the 7-position in the quinazoline ring):

Compounds of the Formula III are commercially available or may be prepared using standard techniques, for example as illustrated in US 5,252,586 and WO 94/27965.

Compounds of the Formula IV may be prepared using process (e) above, starting with a compound prepared, for example using Process (a).

Compounds of the formula V may be prepared by hydrolysing the corresponding carboxylic ester. The carboxylic ester may be formed for example using similar proceses to process (a) or process (d) from the appropriate carboxylic ester starting materials.

Compounds of the formula VI may be prepared using conventional methods well known in the art. For example the hydroxy protecting group, Pg, in a compound of the formula VIII as hereinbefore described in Reaction Scheme 1 is removed to give the compound of the formula X:



X

The protecting group Pg may be removed from the compound of formula X using conventional techniques.

The compound of the formula X may then be coupled with a compound of the Formula III as hereinbefore defined using analogous conditions to those described in Process (a) or Process (d).

Certain novel intermediates utilised in the above processes are provided as a further feature of the present invention together with the process for their preparation.

Biological Assays

The following assays may be used to measure the effects of the compounds of the present invention as inhibitors of the erb-tyrosine kinases, as inhibitors *in-vitro* of the proliferation of KB cells (human naso-pharangeal carcinoma cells) and as inhibitors *in vivo* on the growth in nude mice of xenografts of LoVo tumour cells (colorectal adenocarcinoma).

a) Protein Tyrosine Kinase phosphorylation Assays

This test measures the ability of a test compound to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by EGFR tyrosine kinase enzyme.

Recombinant intracellular fragments of EGFR, erbB2 and erbB4 (accession numbers X00588, X03363 and L07868 respectively) were cloned and expressed in the baculovirus/Sf21 system. Lysates were prepared from these cells by treatment with ice-cold lysis buffer (20mM N-2-hydroxyethylpiperizine-N'-2-ethanesulfonic acid (HEPES) pH7.5, 150mM NaCl, 10% glycerol, 1% Triton X-100, 1.5mM $MgCl_2$, 1mM ethylene glycol-bis(β-aminoethyl ether) N',N',N',N'-tetraacetic acid (EGTA), plus protease inhibitors and then cleared by centrifugation.

Constitutive kinase activity of the recombinant protein was determined by its ability to phosphorylate a synthetic peptide (made up of a random co-polymer of Glutamic Acid, Alanine and Tyrosine in the ratio of 6:3:1). Specifically, Maxisorb™ 96-well immunoplates were coated with synthetic peptide (0.2μg of peptide in a 100μl phosphate buffered saline (PBS) solution and incubated at 4°C overnight). Plates were washed in PBS-T (phosphate

buffered saline with 0.5% Tween 20) then in 50mM HEPES pH 7.4 at room temperature to remove any excess unbound synthetic peptide. EGFR, ErbB2 or ErbB4 tyrosine kinase activity was assessed by incubation in peptide coated plates for 20 minutes at 22°C in 100mM HEPES pH 7.4, adenosine trisphosphate (ATP) at Km concentration for the respective enzyme, 10mM $MnCl_2$, 0.1mM Na_3VO_4, 0.2mM DL-dithiothreitol (DTT), 0.1% Triton X-100 with test compound in DMSO (final concentration of 2.5%). Reactions were terminated by the removal of the liquid components of the assay followed by washing of the plates with PBS-T.

The immobilised phospho-peptide product of the reaction was detected by immunological methods. Firstly, plates were incubated for 90 minutes at room temperature with anti-phosphotyrosine primary antibodies that were raised in the mouse (4G10 from Upstate Biotechnology). Following extensive washing, plates were treated with Horseradish Peroxidase (HRP) conjugated sheep anti-mouse secondary antibody (NXA931 from Amersham) for 60 minutes at room temperature. After further washing, HRP activity in each well of the plate was measured colorimetrically using 22'-Azino-di-[3-ethylbenzthiazoline sulfonate (6)] diammonium salt crystals (ABTS™ from Roche) as a substrate. Quantification of colour development and thus enzyme activity was achieved by the measurement of absorbance at 405nm on a Molecular Devices ThermoMax microplate reader. Kinase inhibition for a given compound was expressed as an IC_{50} value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of phosphorylation in this assay. The range of phosphorylation was calculated from the positive (vehicle plus ATP) and negative (vehicle minus ATP) control values.

b) EGFR driven KB cell proliferation assay

This assay measures the ability of a test compound to inhibit the proliferation of KB cells (human naso-pharangeal carcinoma obtained from the American Type Culture Collection (ATCC).

KB cells (human naso-pharangeal carcinoma obtained from the ATCC were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% foetal calf serum, 2 mM glutamine and non-essential amino acids at 37°C in a 7.5% CO_2 air incubator. Cells were harvested from the stock flasks using Trypsin/ethylaminediaminetetraacetic acid (EDTA). Cell density was measured using a haemocytometer and viability was calculated using trypan blue solution before being seeded at a density of 1.25×10^3 cells per well of a 96 well plate in

DMEM containing 2.5% charcoal stripped serum, 1mM glutamine and non-essential amino acids at 37°C in 7.5% CO_2 and allowed to settle for 4 hours.

Following adhesion to the plate, the cells are treated with or without EGF (final concentration of 1ng/ml) and with or without compound at a range of concentrations in dimethylsulfoxide (DMSO) (0.1% final) before incubation for 4 days. Following the incubation period, cell numbers were determined by addition of 50µl of 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (stock 5mg/ml) for 2 hours. MTT solution was then tipped off, the plate gently tapped dry and the cells dissolved upon the addition of 100µl of DMSO.

Absorbance of the solubilised cells was read at 540nm using a Molecular Devices ThermoMax microplate reader. Inhibition of proliferation was expressed as an IC_{50} value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of proliferation. The range of proliferation was calculated from the positive (vehicle plus EGF) and negative (vehicle minus EGF) control values.

c) H16N-2 cell proliferation assay

This assay measures the ability of a test compound to inhibit heregulin □ or EGF driven proliferation of H16N-2 cells. These non-neoplastic eptihelial cells respond in a proliferative manner to stimulation with either EGF or heregulin □ (Ram, G.R.and Ethier, S.P.(1996) *Cell Growth and Differentiation*, 7, 551-561) were isolated human mammary tissue (Band, V. and Sager, R. Tumour progression in breast cancer. In: J. S. Rhim and A. Dritschilo (eds.), *Neoplastic Transformation in human Cell Culture*, pp 169-178. Clifton, NJ: Humana Press, 1991) and were obtained from the Dana-Farber Cancer Institute, 44 Binney Street, Boston, Massachusetts 02115.

H16N-2 cells were routinely cultured in culture medium (a 1:1 mix of Gibco F12 and Ham's □MEM media containing 1 % foetal calf serum, 10mM HEPES, 1µg/ml Insulin, 12.5ng/ml EGF, 2.8µM Hydrocortisone, 2nM Estradiol 5µM Ascorbic Acid, 10µg/ml Transferrin, 0.1mM Phosphoethanolamine, 15nM Sodium Selenite, 2mM Glutamine, 10nM Tri-iodo-thrynoine, 35µg/ml Bovine pituitary Extract and 0.1mM Ethanolamine) at 37°C in a 7.5% CO_2 air incubator. Cells were harvested from the stock flasks using Trypsin/ethylaminediaminetetraacetic acid (EDTA). Cell density was measured using a haemocytometer and viability was calculated using trypan blue solution before being seeded at

a density of $1.0x10^3$ cells per well of a 96 well plate in the above media at 37°C in 7.5% CO_2 and allowed to settle for 72 hours.

Following this, the cells were starved of serum for 24 hours upon the addition of starvation medium (a 1:1 mix of Gibco F12 and Ham's □MEM media containing, 10mM HEPES, 2nM Estradiol, 5μM Ascorbic Acid, 10μg/ml Transferrin, 0.1mM Phosphoethanolamine, 15nM Sodium Selenite, 2mM Glutamine, and 0.1mM Ethanolamine) and incubated at 37°C in 7.5% CO_2. The cells were then treated with or without compound at a range of concentrations in dimethylsulphoxide (DMSO) (1% final) for two hours before the addition of exogenous ligand (at a final concentration of 100ng/ml of heregulin □ or 5ng/ml of EGF) and incubation with both ligand and compound for 4 days at 37°C in 7.5% CO_2. Following the incubation period, cell numbers were determined by removal of the media by aspiration and incubating with 50μl of 3-(4,5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) (stock 5mg/ml) for 2 hours. MTT solution was then removed by aspiration, allowed to air dry and the cells dissolved upon the addition of 100μl of DMSO. Absorbance of this solubilised cells was read at 540nm to quantify cell biomass. Inhibition of proliferation was expressed as an IC_{50} value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of proliferation. The range of proliferation was calculated from the positive (vehicle plus ligand) and negative (vehicle minus ligand) control values.

d) *In vivo* Xenograft assay

This assay measures the ability of a test compound to inhibit the growth of a LoVo tumour (colorectal adenocarcinoma obtained from the ATCC) in Female Swiss athymic mice (Alderley Park, *nu/nu* genotype).

Female Swiss athymic (*nu/nu* genotype) mice were bred and maintained in Alderley Park in negative pressure Isolators (PFI Systems Ltd.). Mice were housed in a barrier facility with 12hr light/dark cycles and provided with sterilised food and water *ad libitum*. All procedures were performed on mice of at least 8 weeks of age. LoVo tumour cell (colorectal adenocarcinoma obtained from the ATCC) xenografts were established in the hind flank of donor mice by sub cutaneous injections of $1x10^7$ freshly cultured cells in 100μl of serum free media per animal. On day 5 post-implant, mice were randomised into groups of 7 prior to the treatment with compound or vehicle control that was administered once daily at 0.1ml/10g body weight. Tumour volume was assessed twice weekly by bilateral Vernier calliper

measurement, using the formula (length x width) x √(length x width) x □6), where length was the longest diameter across the tumour, and width was the corresponding perpendicular. Growth inhibition from start of study was calculated by comparison of the mean changes in tumour volume for the control and treated groups, and statistical significance between the two groups was evaluated using a Students *t* test.

e) hERG-encoded Potassium Channel Inhibition Assay

This assay determines the ability of a test compound to inhibit the tail current flowing through the human ether-a-go-go-related-gene (hERG)-encoded potassium channel.

Human embryonic kidney (HEK) cells expressing the hERG-encoded channel were grown in Minimum Essential Medium Eagle (EMEM; Sigma-Aldrich catalogue number M2279), supplemented with 10% Foetal Calf Serum (Labtech International; product number 4-101-500), 10% M1 serum-free supplement (Egg Technologies; product number 70916) and 0.4 mg/ml Geneticin G418 (Sigma-Aldrich; catalogue number G7034). One or two days before each experiment, the cells were detached from the tissue culture flasks with Accutase (TCS Biologicals) using standard tissue culture methods. They were then put onto glass coverslips resting in wells of a 12 well plate and covered with 2 ml of the growing media.

For each cell recorded, a glass coverslip containing the cells was placed at the bottom of a Perspex chamber containing bath solution (see below) at room temperature (~20 °C). This chamber was fixed to the stage of an inverted, phase-contrast microscope. Immediately after placing the coverslip in the chamber, bath solution was perfused into the chamber from a gravity-fed reservoir for 2 minutes at a rate of ~ 2 ml/min. After this time, perfusion was stopped.

A patch pipette made from borosilicate glass tubing (GC120F, Harvard Apparatus) using a P-97 micropipette puller (Sutter Instrument Co.) was filled with pipette solution (see hereinafter). The pipette was connected to the headstage of the patch clamp amplifier (Axopatch 200B, Axon Instruments) via a silver/silver chloride wire. The headstage ground was connected to the earth electrode. This consisted of a silver/silver chloride wire embedded in 3% agar made up with 0.85% sodium chloride.

The cell was recorded in the whole cell configuration of the patch clamp technique. Following "break-in", which was done at a holding potential of –80 mV (set by the amplifier), and appropriate adjustment of series resistance and capacitance controls, electrophysiology software (*Clampex*, Axon Instruments) was used to set a holding potential (-80 mV) and to

deliver a voltage protocol. This protocol was applied every 15 seconds and consisted of a 1 s step to +40 mV followed by a 1 s step to –50 mV. The current response to each imposed voltage protocol was low pass filtered by the amplifier at 1 kHz. The filtered signal was then acquired, on line, by digitising this analogue signal from the amplifier with an analogue to digital converter. The digitised signal was then captured on a computer running *Clampex* software (Axon Instruments). During the holding potential and the step to + 40 mV the current was sampled at 1 kHz. The sampling rate was then set to 5 kHz for the remainder of the voltage protocol.

The compositions, pH and osmolarity of the bath and pipette solution are tabulated below.

Salt	Pipette (mM)	Bath (mM)
NaCl	-	137
KCl	130	4
$MgCl_2$	1	1
$CaCl_2$	-	1.8
HEPES	10	10
glucose	-	10
Na_2ATP	5	-
EGTA	5	-

Parameter	Pipette	Bath
pH	7.18 – 7.22	7.40
pH adjustment with	1M KOH	1M NaOH
Osmolarity (mOsm)	275-285	285-295

The amplitude of the hERG-encoded potassium channel tail current following the step from +40 mV to –50 mV was recorded on-line by *Clampex* software (Axon Instruments). Following stabilisation of the tail current amplitude, bath solution containing the vehicle for the test substance was applied to the cell. Providing the vehicle application had no significant effect on tail current amplitude, a cumulative concentration effect curve to the compound was then constructed.

The effect of each concentration of test compound was quantified by expressing the tail current amplitude in the presence of a given concentration of test compound as a percentage of that in the presence of vehicle.

Test compound potency (IC_{50}) was determined by fitting the percentage inhibition values making up the concentration-effect to a four parameter Hill equation using a standard data-fitting package. If the level of inhibition seen at the highest test concentration did not exceed 50%, no potency value was produced and a percentage inhibition value at that concentration was quoted.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b) and (c):-

Test (a):- IC_{50} in the range, for example, 0.001 - 10 μM;

Test (b):- IC_{50} in the range, for example, 0.001 - 10 μM;

Test (c):- IC_{50} in the range, for example, 0.001 - 10 μM;

Test (d):- activity in the range, for example, 1-200 mg/kg/day;

No physiologically unacceptable toxicity was observed in Test (c) at the effective dose for compounds tested of the present invention. Accordingly no untoward toxicological effects are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore is administered at the dosage ranges defined hereinafter.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using

conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

We have found that the compounds of the present invention possess anti-proliferative properties such as anti-cancer properties that are believed to arise from their erbB family receptor tyrosine kinase inhibitory activity, particularly inhibition of the EGF receptor (erbB1) tyrosine kinase. Furthermore, certain of the compounds according to the present invention possess substantially better potency against the EGF receptor tyrosine kinase, than against other tyrosine kinase enzymes, for example erbB2. Such compounds possess sufficient potency against the EGF receptor tyrosine kinase that they may be used in an amount sufficient to inhibit EGF receptor tyrosine kinase whilst demonstrating little, or significantly lower, activity against other tyrosine kinase enzymes such as erbB2. Such compounds are

likely to be useful for the selective inhibition of EGF receptor tyrosine kinase and are likely to be useful for the effective treatment of, for example EGF driven tumours.

Accordingly, the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by erbB receptor tyrosine kinases (especially EGF receptor tyrosine kinase), i.e. the compounds may be used to produce an erbB receptor tyrosine kinase inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for the treatment of malignant cells characterised by inhibition of one or more of the erbB family of receptor tyrosine kinases. Particularly the compounds of the invention may be used to produce an anti-proliferative and/or pro-apoptotic and/or anti-invasive effect mediated alone or in part by the inhibition of erbB receptor tyrosine kinases. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours that are sensitive to inhibition of one or more of the erbB receptor tyrosine kinases, such as EGF and/or erbB2 and/or erbB4 receptor tyrosine kinases (especially EGF receptor tyrosine kinase) that are involved in the signal transduction steps which drive proliferation and survival of these tumour cells. Accordingly the compounds of the present invention are expected to be useful in the treatment of psoriasis, benign prostatic hyperplasia (BPH), atherosclerosis and restenosis and/or cancer by providing an anti-proliferative effect, particularly in the treatment of erbB receptor tyrosine kinase sensitive cancers. Such benign or malignant tumours may affect any tissue and include non-solid tumours such as leukaemia, multiple myeloma or lymphoma, and also solid tumours, for example bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancers.

According to this aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament.

According to a further aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

Thus according to this aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of erbB receptor tyrosine kinases, such as EGFR and/or erbB2 and/or erbB4 (especially EGFR), that are involved in the signal transduction steps which lead to the proliferation of tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of one or more of the erbB family of receptor tyrosine kinases, such as EGFR and/or erbB2 and/or erbB4 (especially EGFR), that are involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, for use in the prevention or treatment of those tumours which are sensitive to inhibition of erbB receptor tyrosine kinases, such as EGFR and/or erbB2 and/or erbB4 (especially EGFR), that are involved in the signal transduction steps which lead to the proliferation of tumour cells.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a EGFR and/or erbB2 and/or erbB4 (especially a EGFR) tyrosine kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a EGFRand/or an erbB2 and or an erbB4 (especially a EGFR) tyrosine kinase inhibitory effect which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, for use in providing a EGFR and/or erbB2 and/or erbB4 (especially a EGFR) tyrosine kinase inhibitory effect.

According to a further feature of the present invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a selective EGFR tyrosine kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a selective EGFR tyrosine kinase inhibitory effect which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, for use in providing a selective EGFR tyrosine kinase inhibitory effect.

By "a selective EGFR kinase inhibitory effect" is meant that the quinazoline derivative of Formula I is more potent against EGF receptor tyrosine kinase than it is against other kinases. In particular some of the compounds according to the invention are more potent against EGF receptor kinase than it is against other tyrosine kinases such as other erbB receptor tyrosine kinases such erbB2 . For example a selective EGFR kinase inhibitor according to the invention is at least 5 times, preferably at least 10 times more potent against erbB2 receptor tyrosine kinase driven proliferation than it is against EGFR tyrosine kinase driven proliferation, as determined from the relative IC_{50} values in a suitable assay (for example the H116N-2 assay described above).

According to a further aspect of the present invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a cancer (for example a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer).

According to a further feature of this aspect of the invention there is provided a method for treating a cancer (for example a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial,

gastric, head and neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer) in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of a cancer (for example selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer).

As mentioned above the size of the dose required for the therapeutic or prophlyactic treatment of a particular disease will necessarily be varied depending upon, amongst other things, the host treated, the route of administration and the severity of the illness being treated.

The anti-proliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as

anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example other inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the Formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of the erbB receptor tyrosine protein kinases. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated by the following examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulf
ate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and / or analytical LCMS, and reaction times are given for illustration only;

(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz or 400MHzusing perdeuterio dimethyl sulfoxide (DMSO-d_6) as solvent unless otherwise indicated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) solvent ratios are given in volume:volume (v/v) terms; and

(x) mass spectra (MS) were run using a Waters or Micromass electrospray LC-MS in positive or negative ion mode; values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is $(MH)^+$;

(xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulfur atom have not been resolved;

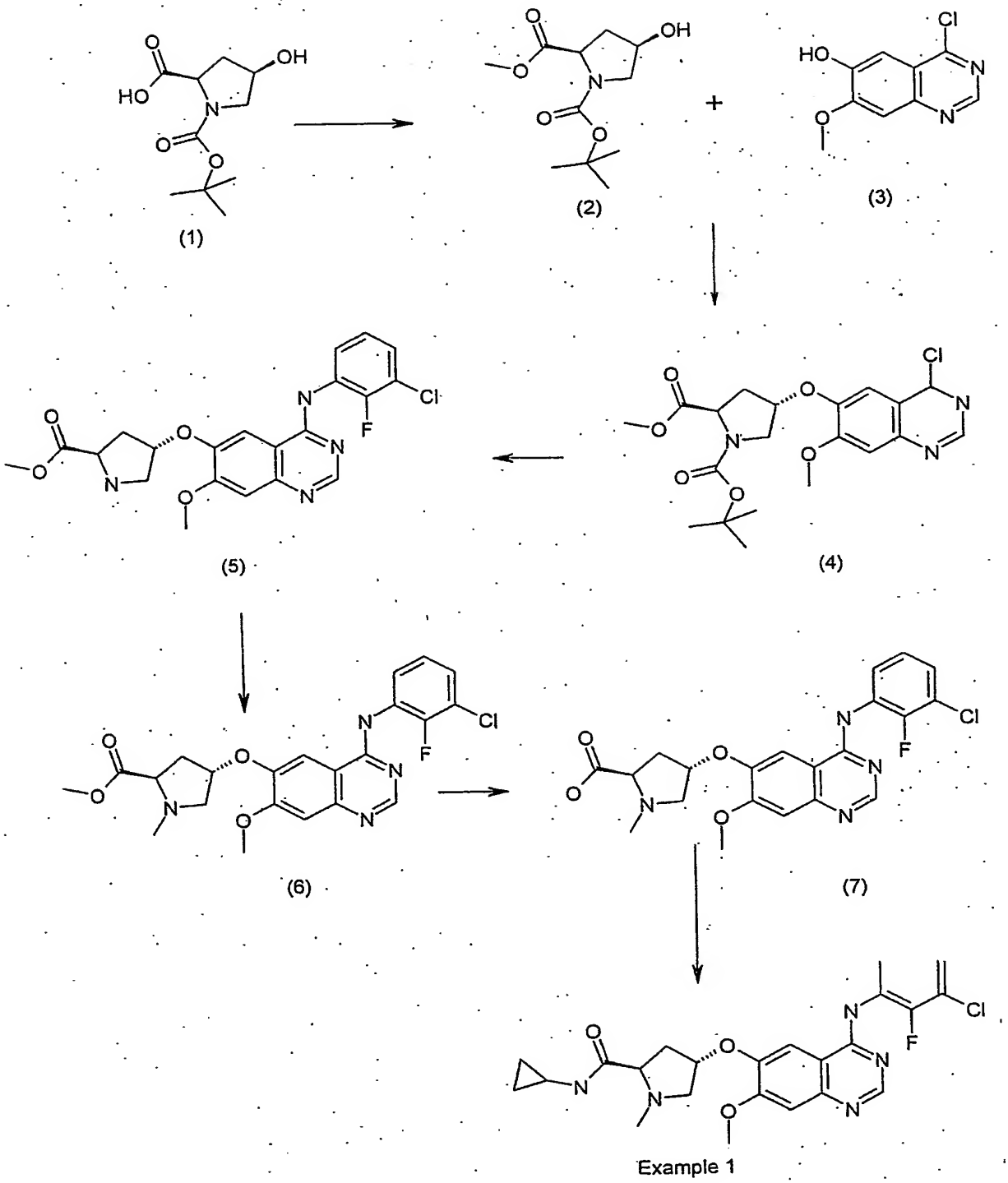
(xii) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;

(xvi) the following abbreviations have been used:

DMF	*N,N*-dimethylformamide;
DMA	*N,N*-dimethylacetamide;
THF	tetrahydrofuran;
DIPEA	diisopropylethylamine
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate

xvii) where a synthesis is described as leading to an acid addition salt (e.g. HCl salt), the specific stoichiometry of the salt was not confirmed.

Example 1



(4*S*)-4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*-cyclopropyl-1-methyl-D-prolinamide

HATU (0.23g) was added to an agitated solution of (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-D-proline (0.18g), cyclopropylamine (34.4mg) and DIPEA (156mg) in methylene chloride (5ml). After 16hrs the reaction mixture was reduced in vacuo. The residues were re-dissolved in methylene chloride and washed with sodium hydroxide solution (2M) and water. The organic phase was then purified by column chromatography on silica eluting with increasingly polar mixtures of methanol/methylene chloride (0/100-10/90). The fractions containing the desired product were combined and evaporated to a foam which was triturated with diethylether to give the title compound as a white solid. (0.15g). ^{1}H NMR Spectrum: (DMSO d_6) 0.40 – 0.48 (m, 2H), 0.57 - 0.64 (m, 2H), 2.05 – 2.14 (m, 1H), 2.28 (s, 3H), 2.33 – 2.45 (m, 1H), 2.48 – 2.56 (m, 1H + DMSO), 2.61 – 2.70 (m, 1H), 3.08 (t, 1H), 3.64 (dd, 1H), 3.94 (s, 3H), 5.06 (m, 1H), 7.20 (s, 1H), 7.28 (t, 1H), 7.44 – 7.56 (m, 2H), 7.65 (s, 1H), 7.87 (d, 1H), 8.35 (s, 1H), 9.63 (s, 1H); Mass Spectrum: $(M+H)^+$ 486.44

The starting material 1,2-Pyrrolidinedicarboxylic acid, 4-hydroxy-, 1-(1,1-dimethylethyl) 2-methyl ester, (2R,4R) (**2**) was prepared as follows:

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (14.73 g) was added to a stirred suspension of 1,2-pyrrolidinedicarboxylic acid, 4-hydroxy-, 1-(1,1-dimethylethyl) ester, (2R,4R) (**1**) (13.65 g), dimethylaminopyridine (21.65 g) and methanol (5.67 g) in methylene chloride (400 ml) and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was washed with citric acid (1.0 M), saturated aqueous sodium bicarbonate solution and saturated brine, dried over $MgSO_4$, filtered and evaporated. The residues were then purified by column chromatography on silica eluting with increasingly polar mixtures of methanol/methylene chloride (1/99-5/95). The desired product fractions were combined and evaporated to give 1,2-pyrrolidinedicarboxylic acid, 4-hydroxy-, 1-(1,1-dimethylethyl) 2-methyl ester, (2R,4R) (**2**) as a white crystalline solid, (5.9 g). ^{1}H NMR Spectrum: (DMSO d_6) 1.32 + 1.38 (2s, 9H), 1.76 – 1.87 (m, 1H), 2.24 – 2.28 (m, 1H), 3.06 – 3.15 (m, 1H), 3.42 – 3.51 (m, 1H), 3.60 + 3.63 (2s, 3H), 4.15 – 4.24 (m, 2H), 4.92 – 5.00 (m, 1H).

Starting material 1,2-Pyrrolidinedicarboxylic acid, 4-hydroxy-1-(1,1-dimethylethyl) ester, (2R,4R), (**1**), (Boc-D-cis-hyp-OH) is commercially available.

Starting material (**3**) was prepared as follows:

6-Acetoxy-4-chloro-7-methoxyquinazoline, (Example 25-5 of in WO01/66099;10.0g, 39.6 mmole) was added in portions to a stirred 7N methanolic ammonia solution (220 ml) cooled to 10°C in an ice/water bath. After stirring for one hour the precipitate was filtered, washed with diethylether and dried thoroughly under high vacuum to give 4-chloro-7-methoxyquinazolin-6-ol (**3**) (5.65g, 67.8%); ^{1}H NMR Spectrum: (DMSO d_6) 3.96 (s, 3H); 7.25 (s, 1H); 7.31 (s, 1H); 8.68 (s, 1H); Mass Spectrum: $(M+H)^+$ 211.

The starting material (**4**) was prepared as follows:

Di-ethyl azodicarboxylate (5.71g) was added slowly to a stirred suspension of 1,2-pyrrolidinedicarboxylic acid, 4-hydroxy-, 1-(1,1-dimethylethyl) 2-methyl ester, (2R,4R) (**2**) (5.9g), 4-chloro-7-methoxyquinazolin-6-ol (**3**) (4.6g) and triphenylphosphine(8.6g) in methylene chloride (400 ml)at 25°C under an atmosphere of nitrogen and the reaction mixture was stirred for 2 hours. The reaction mixture was then evaporated to ½ volume and purified by column chromatography on silica eluting with increasingly polar mixtures of methanol/methylene chloride (1/99-3/97). The desired product fractions were combined and evaporated to give 1-*tert*-butyl 2-methyl (2*R*, 4*S*)-4-[(4-chloro-7-methoxyquinazolin-6-yl)oxy]pyrrolidine-1,2-dicarboxylate (**4**) as a pale yellow gum.
This was used in the preparation of (**5**) without further purification.

The starting material methyl (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-D-prolinate hydrochloride (**5**) was prepared as follows:
4.0M HCl in Dioxane (15 ml) was added to a suspension of 1-*tert*-butyl 2-methyl (2*R*, 4*S*)-4-[(4-chloro-7-methoxyquinazolin-6-yl)oxy]pyrrolidine-1,2-dicarboxylate (**4**) and 3-chloro-2-fluoroaniline (2.89g) in acetonitrile (400 ml) and the reaction mixture was stirred and heated at 70°C for 3 hours. The resulting precipitate was filtered hot and washed with acetonitrile and diethylether and dried under vacuum to give methyl (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-D-prolinate hydrochloride (**5**) as an off-white solid, (6.3g). ^{1}H NMR Spectrum: (DMSO d_6) 2.46 – 2.60 (m, 2H), 3.37 – 3.46 (m, 1H), 3.71 (s, 3H), 3.89 – 3.98 (m, 4H), 4.53 (t, 1H), 5.42 (m, 1H), 7.29 (t, 1H), 7.38 – 7.48

(m, 2H), 7.55 (t, 1H), 8.64 (s, 1H), 8.75 (s, 1H), 12.28 (bs, 1H); Mass Spectrum: $(M+H)^+$ 446.96

Compound (6) was prepared as follows:

Methyl (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-D-prolinate hydrochloride (5) (6.3g), paraformaldehyde (3.9g), sodium cyanoborohydride (3.28g) and magnesium sulphate (3.13g) were suspended in methanol (50ml) and heated to 45°C for 4 hours under an atmosphere of nitrogen. The reaction mixture was filtered, evaporated and partitioned between ethylacetate and saturated aqueous sodium bicarbonate solution. The organics were then washed with saturated brine, dried over $MgSO_4$, filtered and evaporated. The residues were then purified by column chromatography on silica eluting with increasingly polar mixtures of methanol/methylene chloride (2-3%) to give methyl (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-D-prolinate as a yellow foam,(4.19 g). ^{1}H NMR Spectrum: (DMSO d_6) 2.14 – 2.23 (m, 1H), 2.34 (s, 3H), 2.53 – 2.60 (m, 2H), 3.36 (t, 1H), 3.61 (dd, 1H), 3.66 (s, 3H), 3.94 (s, 3H), 5.08 (m, 1H), 7.20 (s, 1H), 7.27 (t, 1H), 7.44 – 7.54 (m, 2H), 7.68 (s, 1H), 8.36 (s, 1H), 9.62 (s, 1H); Mass Spectrum : $(M+H)^+$ 460.9

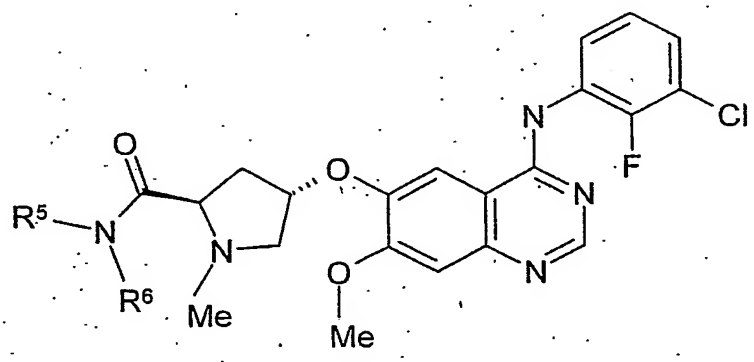
Compound (7) was prepared as follows:

Sodium hydroxide 2M (7 ml) was added to a stirred solution of methyl (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-D-prolinate (4.18g) in methanol (20 ml) and THF (10 ml) at 25^{0}C and the reaction mixture was stirred for 4 hours. The reaction mixture was evaporated and the residue re-dissolved in water. The pH of this solution was then adjusted to 6 by the dropwise addition of 2M HCl (aq) to give (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-1-methyl-D-proline as a pale yellow solid which was filtered and washed with water and dried, (3.5 g). ^{1}H NMR Spectrum: (DMSO d_6) 2.21 – 2.31 (m, 1H), 2.35 – 2.49 (m, 1H), 2.50 (s, 3H), 2.78 (dd, 1H), 3.42 (t, 1H), 3.77 (dd, 1H), 3.94 (s, 3H), 5.08 (m, 1H), 7.20 (s, 1H), 7.27 (t, 1H), 7.44 – 7.54 (m, 2H), 7.74 (s, 1H), 8.37 (s, 1H), 9.75 (s, 1H); Mass Spectrum: $(M+H)^+$ 446.9

Example 2

The following compounds were all made from Compound (7) in a similar manner to that of Example 1 from the appropriate amine hydrochlroride.

Table 1



Compound	R^5	R^6	Footnote
1	H	cyclopropylmethyl	a
2	H	$CH_3OCH_2CH_2$-	b
3	H	cyclopentylmethyl	c
4	Me	$CH_3OCH_2CH_2$	d
5	H	-OMe	e
6	H	cyclohexyl	f
7	H	tetrahydro-2H-pyran-4-yl	g

Footnotes

a) ^{1}H NMR Spectrum: (DMSO d_6) 0.14 – 0.20 (m, 2H), 0.37 - 0.44 (m, 2H), 0.94 (m, 1H), 2.10 – 2.21 (m, 1H), 2.34 (s, 3H), 2.31 – 2.44 (m, 1H), 2.56 (dd, 1H), 2.95 – 3.03 (m, 2H), 3.14 (t, 1H), 3.69 (dd, 1H), 3.94 (s, 3H), 5.08 (m, 1H), 7.23 (s, 1H), 7.29 (t, 1H), 7.45 – 7.56 (m, 2H), 7.68 (s, 1H), 7.88 (t, 1H), 8.38 (s, 1H), 9.64 (s, 1H); Mass Spectrum: $(M+H)^+$ 500.48.

b) ^{1}H NMR Spectrum: (DMSO d_6) 2.10 – 2.19 (m, 1H), 2.29 – 2.40 (m, 1H), 2.31 (s, 3H), 2.48 – 2.58 (m, 1H + DMSO), 3.13 (t, 1H), 3.21 – 3.29 (m, 2H), 3.24 (s, 3H), 3.34 – 3.38 (m, 2H), 3.68 (dd, 1H), 3.94 (s, 3H), 5.06 (m, 1H), 7.20 (s, 1H), 7.27 (t, 1H), 7.44 – 7.55 (m, 2H), 7.68 (s, 1H), 7.82 (t, 1H), 8.36 (s, 1H), 9.62 (s, 1H); Mass Spectrum: $(M+H)^+$ 504.51.

c) ^{1}H NMR Spectrum: (DMSO d_6) 1.32 – 1.68 (m, 6H), 1.74 – 1.86 (m, 2H), 2.06 – 2.15 (m, 1H), 2.30 (s, 3H), 2.33 – 2.44 (m, 1H), 2.49 – 2.57 (m, 1H + DMSO), 3.13 (t, 1H), 3.66 (dd, 1H), 3.94 (s, 3H), 4.02 (q, 1H), 5.08 (m, 1H), 7.20 (s, 1H), 7.29 (t, 1H), 7.45 – 7.56 (m, 2H), 7.67 (s, 1H), 7.74 (d, 1H), 8.36 (s, 1H), 9.62 (s, 1H); Mass Spectrum: $(M+H)^+$ 514.54.

d) ^{1}H NMR Spectrum: (DMSO d_6) 2.07 – 2.18 (m, 1H), 2.27 – 2.34 (m, 3H), 2.56 – 2.67 (m, 1H), 2.83 – 2.90 (m, 4H), 3.21 – 3.26 (d, 3H), 3.40 – 3.48 (m, 3H), 3.54 – 3.88 (m, 3H), 3.93 (s, 3H), 5.10 (m, 1H), 7.20 (s, 1H), 7.27 (t, 1H), 7.44 – 7.55 (m, 2H), 7.68 (d, 1H), 8.36 (s, 1H), 9.65 (s, 1H); Mass Spectrum: $(M+H)^+$ 518.56.

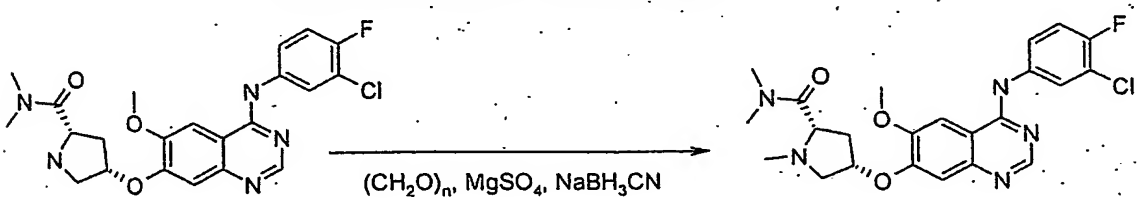
e) ^{1}H NMR Spectrum: (DMSO d_6) 2.08 – 2.17 (m, 1H), 2.33 (s, 3H), 2.40 – 2.64 (m, 2H + DMSO), 3.08 – 3.16 (m, 1H), 3.58 – 3.70 (m, 1H), 3.60 (s, 3H), 3.94 (s, 3H), 5.08 (m, 1H), 7.20 (s, 1H), 7.27 (t, 1H), 7.44 – 7.55 (m, 2H), 7.68 (d, 1H), 8.36 (s, 1H), 9.68 (s, 1H), 11.23 (s, 1H); Mass Spectrum: $(M+H)^+$ 475.99

f) ^{1}H NMR Spectrum: (DMSO d_6) 1.08 – 1.34 (m, 6H), 1.60 – 1.77 (m, 4H), 2.07 – 2.16 (m, 1H), 2.30 (s, 3H), 2.25 – 2.58 (m, 2H + DMSO), 3.12 (t, 1H), 3.51 – 3.60 (m, 1H), 3.68 (dd, 1H), 3.92 (s, 3H), 5.08 (m, 1H), 7.20 (s, 1H), 7.27 (t, 1H), 7.44 – 7.55 (m, 2H), 7.61 (d, 1H), 7.67 (s, 1H), 8.37 (s, 1H), 9.64 (s, 1H); Mass Spectrum: $(M+H)^+$ 528.63

g) ^{1}H NMR Spectrum: (DMSO d_6) 1.37 – 1.53 (m, 2H), 1.61 – 1.70 (m, 2H), 2.08 – 2.17 (m, 1H), 2.30 (s, 3H), 2.34 – 2.59 (m, 2H + DMSO), 3.12 (t, 1H), 3.31 – 3.40 (m, 2H), 3.67 (dd, 1H), 3.75 – 3.85 (m, 3H), 3.94 (s, 3H), 5.06 (m, 1H), 7.20 (s, 1H), 7.27 (t, 1H), 7.44 – 7.55 (m, 2H), 7.68 (s, 1H), 7.78 (d, 1H), 8.36 (s, 1H), 9.63 (s, 1H); Mass Spectrum: $(M+H)^+$ 530.59.

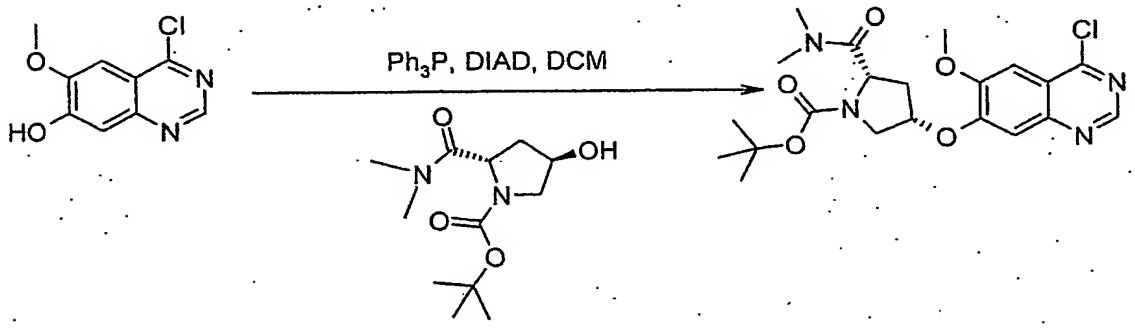
Example 3

(4*S*)-4-({4-[(3-Chloro-4-fluorophenyl)amino]-6-methoxyquinazolin-7-yl}oxy)-*N*,*N*,1-trimethyl-L-prolinamide



(4*S*)-4-({4-[(3-Chloro-4-fluorophenyl)amino]-6-methoxyquinazolin-7-yl}oxy)-*N*,*N*-dimethyl-L-prolinamide (50mg, 0.11mmol) was dissolved in methanol (5ml) and magnesium sulphate (26mg, 0.22mmol), paraformaldehyde (33mg, 1.09mmol) and sodium cyanoborohydride (27mg, 0.44mmol) added. The mixture was heated at 50°C for 2h, cooled, filtered and concentrated under reduced pressure. Column chromatography of the residue (5% 7N ammonia in methanol/dichloromethane) gave (4*S*)-4-({4-[(3-chloro-4-fluorophenyl)amino]-6-methoxyquinazolin-7-yl}oxy)-*N*,*N*,1-trimethyl-L-prolinamide (44mg, 85%) as a white solid. ^{1}H NMR spectrum: (DMSO d_6) 1.82 (m, 1H); 2.23 (s, 3H); 2.60 (m, 1H); 2.83 (m, 4H); 3.08 (s, 3H); 3.22 (m, 2H); 3.97 (s, 3H); 5.07 (m, 1H); 7.09 (s, 1H); 7.45 (t, 1H); 7.82 (m, 2H); 8.14 (s, 1H); 8.50 (s, 1H); 9.55 (s, 1H); Mass Spectrum: $(M+H)^+$ 474

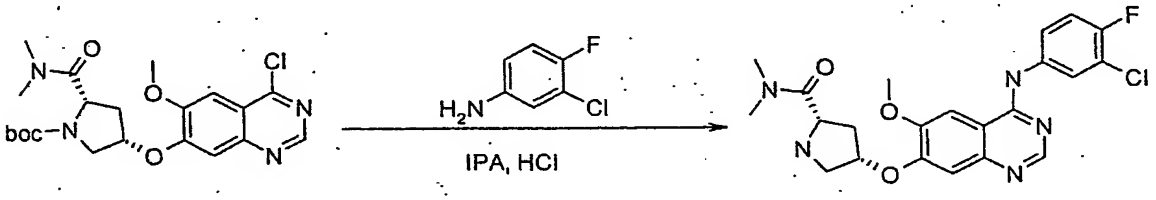
The starting material was prepared as follows:



4-Chloro-6-methoxyquinazolin-7-ol (171mg, 0.81mmol), **(2S, 4R)-2-dimethylcarbamoyl-4-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester** (250mg, 0.97mmol) and triphenylphosphine (255mg, 0.97mmol) were stirred in dichloromethane (12ml) and diisopropyl azodicarboxylate (191µl, 0.97mmol) added. The mixture was stirred at room

temperature over night and then concentrated under reduced pressure. Column chromatography eluting with 1:1 ethyl acetate/isohexane gave **(2S, 4S)-4-(4-chloro-6-methoxy-quinazolin-7-yloxy)-2-dimethylcarbamoyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester** (121mg, 33%).

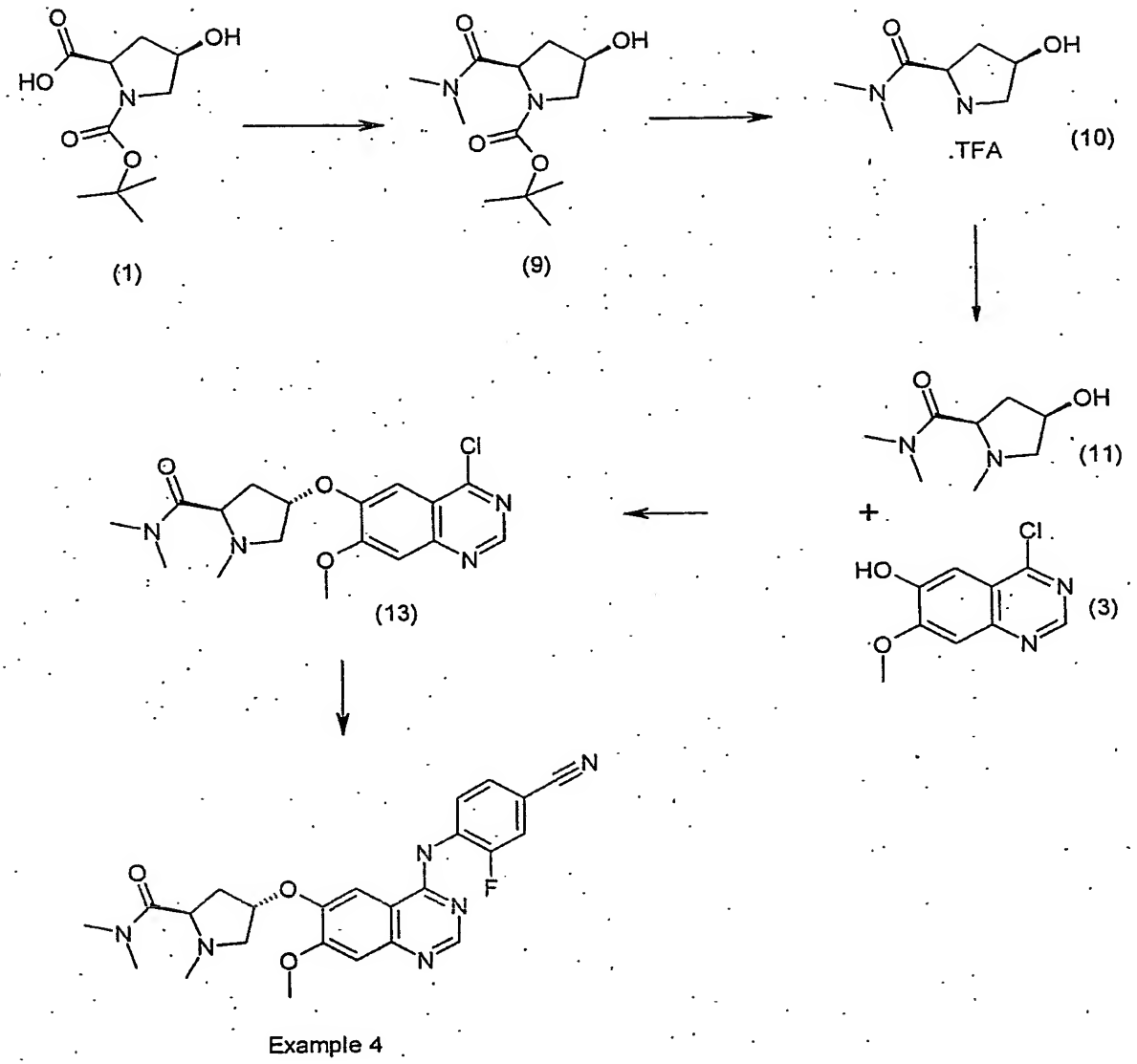
^{1}H NMR spectrum: (DMSO d_6) 1.35 (m, 9H); 1.87 (m, 1H); 2.85 (m, 3H); 3.00 (m, 4H); 3.39 (m, 1H); 3.95 (s, 3H); 4.08 (m, 1H); 4.65 (m, 1H); 5.27 (m, 1H); 7.40 (s, 1H); 7.55 (s, 1H); 8.89 (s, 1H); Mass Spectrum: $(M+Na)^+$ 473.



(2S, 4S)-4-(4-Chloro-6-methoxy-quinazolin-7-yloxy)-2-dimethylcarbamoyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (120mg, 0.27mmol) and 3-chloro-4-fluoroaniline (46mg, 0.32mmol) were stirred in isopropanol (7.5ml) and hydrogen chloride (80µl of a 4M solution in dioxane, 0.32mmol) was added. The mixture was heated at reflux for 2h, cooled and the solid filtered off. This was dissolved in methanol, absorbed onto an Isolute® SCX column washed with methanol and eluted with 7N ammonia in methanol. These were then evaporated and the residues purified by flash chromatography eluting with increasingly polar mixtures of 10% methanol/dichloromethane to 10% 7N ammonia in methanol/dichloromethane to give (4*S*)-4-({4-[(3-chloro-4-fluorophenyl)amino]-6-methoxyquinazolin-7-yl}oxy)-*N*,*N*-dimethyl-L-prolinamide (56mg, 48%) as a white solid.

^{1}H NMR spectrum: (DMSO d_6) 1.68 (m, 1H); 2.71 (m, 1H); 2.85 (s, 3H); 2.95 (dd, 1H); 3.00 (s, 3H); 3.25 (d, 1H); 3.95 (m, 4H); 5.07 (m, 1H); 7.15 (s, 1H); 7.45 (t, 1H); 7.82 (m, 2H); 8.13 (m, 1H); 8.50 (s, 1H); 9.55 (s, 1H); Mass Spectrum: $(M+H)^+$ 460

Example 4



(4*S*)-4-({4-[(4-Cyano-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide

HCl in Dioxan (4.0M, 0.4ml) was added to a stirred solution of (13) (200 mg) 4-amino-3-fluorobenzonitrile (83 mg) in acetonitrile (10 ml) and the reaction mixture was heated at 65^0C for 3 hours.

The resulting precipitate was filtered, washed with acetonitrile then diethyl ether and dried under vacuum to give the title compound as a beige powder solid HCl salt, (210 mg). ^{1}H

NMR Spectrum: (DMSO d_6 + CD_3CO_2D) 2.55 – 2.69 (m, 1H), 2.75 – 2.88 (m, 1H), 2.92 (s, 3H), 2.95 (s, 3H), 2.98 (s, 3H), 3.50 – 3.57 (m, 1H), 4.01 (s, 3H), 4.29 (dd, 1H), 4.94 (dd, 1H), 5.47 (m, 1H), 7.47 (s, 1H), 7.74 – 7.86 (m, 2H), 8.04 (d, 1H), 8.66 (m, 1H), 8.86 (s, 1H); Mass Spectrum: $(M+H)^+$465.

The starting material 1-pyrrolidinecarboxylic acid, 2-[(dimethylamino)carbonyl]-4-hydroxy-, 1,1-dimethylethyl ester, (2*R*,4*R*)- **(9)** was prepared as follows:

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (25.53 g) was added to a stirred suspension of Boc-D-cis-hyp-OH, 1,2-pyrrolidinedicarboxylic acid, 4-hydroxy-1-(1,1-dimethylethyl) ester, (2R,4R) **(1)** (22.0 g), dimethylaminopyridine (58.11 g) and dimethylamine hydrochloride (15.3 g) in methylene chloride (600 ml) and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was washed with citric acid (1.0 M), saturated aqueous sodium bicarbonate solution and saturated brine, dried over magnesium sulphate and filtered. The organic phase was then purified by column chromatography on silica eluting with increasingly polar mixtures of methanol/methylene chloride (1/99-5/95). The desired product fractions were combined and evaporated to give **(9)** as a white crystalline solid, (16.95 g). ^{1}H NMR Spectrum : (DMSO d_6) 1.30 + 1.38 (2s, 9H), 1.50 – 1.61 (m, 1H), 2.31 – 2.42 (m, 1H), 2.83 + 3.02 (2m, 6H), 3.08 – 3.15 (m, 1H), 3.46 – 3.58 (m, 1H), 4.09 – 4.18 (m, 1H), 4.53 – 4.61 (m, 1H), 5.15 – 5.22 (m, 1H).

Starting material Boc-D-cis-hyp-OH (1), 1,2-pyrrolidinedicarboxylic acid, 4-hydroxy-1-(1,1-dimethylethyl) ester, (2R,4R) is commercially available

The starting material **(10)** was prepared as follows:

TFA (20 ml) was added to a stirred solution of 1-pyrrolidinecarboxylic acid, 2-[(dimethylamino)carbonyl]-4-hydroxy-, 1,1-dimethylethyl ester, (2*R*,4*R*)- (9) (5g) in methylene chloride (20 ml) at 25^{0}C under an atmosphere of nitrogen and the reaction mixture was stirred for 1.5 hours. The reaction mixture was then reduced in vacuo and triturated with diethyl ether to give the TFA salt of (4*R*)-4-hydroxy-*N*,*N*-dimethyl-D-prolinamide **(10)** as a white solid. (4.83 g) ^{1}H NMR Spectrum: (DMSO d_6) 1.68 – 1.77 (m, 1H), 2.56 – 2.67 (m, 1H), 2.90 (s, 3H), 2.95 (s, 3H), 3.16 – 3.20 (m, 2H), 4.37 (m, 1H), 4.52 – 4.58 (m, 1H), 5.32 (m, 1H).

The starting material (4*R*)-4-hydroxy-*N*,*N*,1-trimethyl-D-prolinamide (**4**) was prepared as follows:

Platinum oxide was added to a solution of (4*R*)-4-hydroxy-*N*,*N*-dimethyl-D-prolinamide (**10**) (4.83g) in formaldehyde (37 wt % solution in water) (3g), water (16 ml) and acetic acid (30 ml) under an atmosphere of nitrogen. The reaction was then purged with hydrogen and stirred vigorously for 16 hours. The reaction mixture was filtered through celite and reduced in vacuo. The residue was dissolved in methylene chloride and dried over magnesium sulphate. Potassium carbonate (7g) was added and the mixture stirred for one hour. The crudes were filtered and purified by column chromatography on silica eluting with increasingly polar mixtures of methanol (saturated with ammonia) /methylene chloride (5/95-15/85). The fractions containing the desired product were combined and reduced in vacuo to give (4*R*)-4-hydroxy-*N*,*N*,1-trimethyl-D-prolinamide (**11**) as a colourless oil. (2.57g). ^{1}H NMR Spectrum: (DMSO d_6) 1.51 – 1.60 (m, 1H), 2.17 (s, 3H), 2.28 – 2.39 (m, 2H), 2.79 – 2.86 (m, 4H), 3.06 (s, 3H), 3.17 (t, 1H), 4.10 – 4.19 (m, 1H), 4.80 (d, 1H).

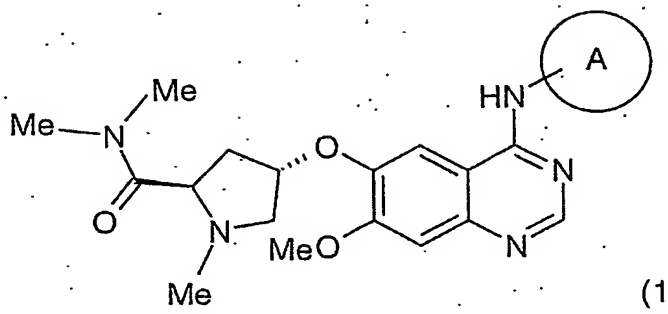
The starting material (4*S*)-4-[(4-chloro-7-methoxyquinazolin-6-yl)oxy]-*N*,*N*,1-trimethyl-D-prolinamide (**13**) was prepared as follows:

Di-ethyl azodicarboxylate (1.38g) was added slowly to a stirred suspension of (4*R*)-4-hydroxy-*N*,*N*,1-trimethyl-D-prolinamide (**11**)(1.0g) , 4-chloro-7-methoxyquinazolin-6-ol (**3**)(1.11g) and triphenylphosphine(2.07g) in methylene chloride (60 ml)at 25^{0}C under an atmosphere of nitrogen and the reaction mixture was stirred for 2 hours. The reaction mixture was then reduced in vacuo to ½ volume, applied to a silica flash column and eluted with increasingly polar mixtures of methanol/methylene chloride (5/95-10/90). The fractions containing the desired product were combined and evaporated to give (4*S*)-4-[(4-chloro-7-methoxyquinazolin-6-yl)oxy]-*N*,*N*,1-trimethyl-D-prolinamide (**13**) as a colourless foam. (1.6g). ^{1}H NMR Spectrum: (DMSO d_6) 2.09 – 2.20 (m, 1H), 2.25 (s, 3H), 2.28 – 2.40 (m, 1H), 2.60 (m, 1H), 2.81 (s, 3H), 3.02 (s, 3H), 3.52 (m, 1H), 3.74 (m, 1H), 3.98 (s, 3H), 5.12 – 5.20 (m, 1H), 7.28 (s, 1H), 7.41 (s, 1H), 8.83 (s, 1H); Mass Spectrum: $(M+H)^+$ 365.4

Examples 5

The compounds in Table 2 were made in an analogous manner to that of Example 4, all HCl salts.

Table 2



(1)

Compound	A	Footnote
1	3-chloro-4-cynanophenyl	a
2	3-chloro-4-(trifluoromethyl)phenyl	b
3	5-chloropyridin-3-yl	c

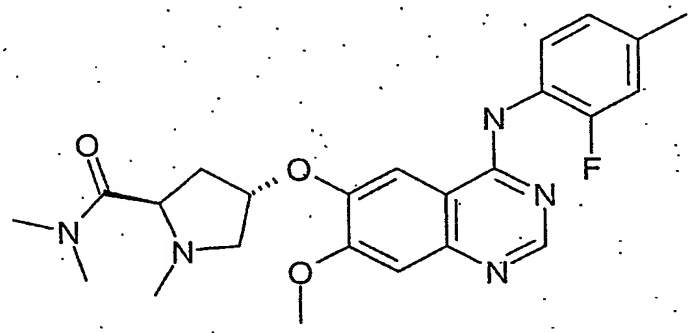
a) ^{1}H NMR Spectrum: (DMSO d_6) 2.54 – 2.66 (m, 1H), 2.70 – 2.86 (m, 1H), 2.94 (s, 3H), 2.96 (s, 3H), 2.98 (s, 3H), 3.49 – 3.57 (m, 1H), 4.00 (s, 3H), 4.26 (dd, 1H), 4.95 (t, 1H), 5.63 (m, 1H), 7.48 (s, 1H), 8.00 (d, 1H), 8.32 (d, 1H), 8.57 (s, 1H), 8.90 (m, 2H), 12.00 (s, 1H); Mass Spectrum: $(M+H)^+$ 481.06.

b) ^{1}H NMR Spectrum: (DMSO d_6) 2.55 – 2.68 (m, 1H), 2.75 – 2.84 (m, 1H), 2.94 (s, 3H), 2.95 (s, 3H), 2.98 (s, 3H), 3.49 – 3.58 (m, 1H), 4.01 (s, 3H), 4.27 (dd, 1H), 4.95 (t, 1H), 5.61 (m, 1H), 7.53 (s, 1H), 7.92 (d, 1H), 8.21 (d, 1H), 8.44 (s, 1H), 8.94 (s, 1H), 8.98 (s ,1H), 12.30 (s, 1H); Mass Spectrum: $(M+H)^+$ 524.04.

c) ^{1}H NMR Spectrum: (DMSO d_6) 2.58 – 2.80 (m, 2H), 2.90 (s, 3H), 2.92 (s, 3H), 2.96 (s, 3H), 3.45 – 3.55 (m, 1H), 3.99 (s, 3H), 4.26 (dd, 1H), 4.92 (t, 1H), 5.57 (m, 1H), 7.54 (s, 1H), 8.48 – 8.51 (m, 2H), 8.92 (s, 1H), 9.01 (s, 1H), 9.10 (s, 1H), 12.66 (s, 1H); Mass Spectrum: $(M+H)^+$ 457.05

Example 6

(4*S*)-4-({4-[(2-Fluoro-4-methylphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide



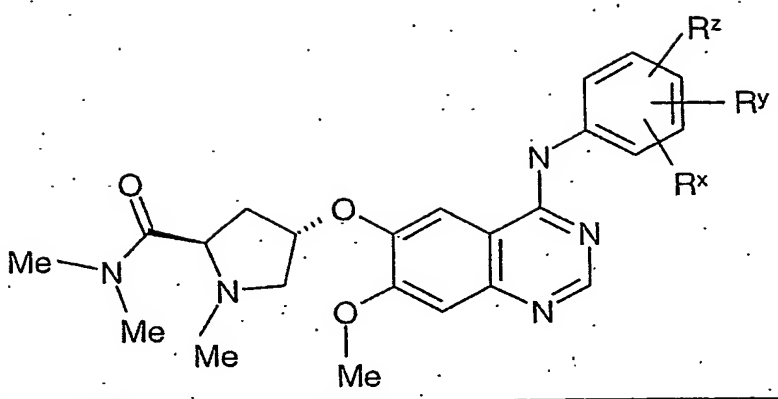
HCl in Dioxan (4.0M, 0.4ml) was added to a stirred solution of (**13**) (200 mg) 2-fluoro-4-methylaniline (76 mg) in acetonitrile (10 ml) and the reaction mixture was heated at 65^{0}C for 3 hours.

The reaction mixture was reduced in vacuo and the residue dissolved in Methanol saturated with ammonia (7N). The solution was then reduced in vacuo and the residue dissolved in methylene chloride and washed with saturated aqueous sodium bicarbonate solution and saturated brine. The organic phase was then purified by column chromatography on silica eluting with increasingly polar mixtures of methanol/methylene chloride (0/100-10/90). The desired product fractions were combined and reduced in vacuo and triturated with diethyl ether to give (4*S*)-4-({4-[(2-fluoro-4-methylphenyl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide as a white solid (175 mg). ^{1}H NMR Spectrum: (DMSO d_6) 2.05 – 2.18 (m, 1H), 2.30 (s, 3H), 2.35 (s, 3H), 2.44 – 2.53 (m, 2H + DMSO), 2.83 (s, 3H), 3.04 (s, 3H), 3.59 – 3.77 (m, 2H), 3.94 (s, 3H), 5.08 (m, 1H), 7.02 – 7.19 (m, 3H), 7.31 – 7.40 (m, 1H), 7.68 (s, 1H), 8.28 (s, 1H), 9.43 (s, 1H); Mass Spectrum : $(M+H)^+$ 454.

Example 7

The following compounds were made in an analogous manner to that of Example 6.

Table 3



Compound	R^x	R^y	R^z	Footnotes
1	3-Cl	4-F	H	a
2	2-F	4-OH	H	b
3	2-F	4-F	H	c
4	2-F	5-F	H	d
5	2-F	5-Cl	H	e
6	2-F	4-Cl	H	f
7	2-OH	5-Cl	H	g
8	3-Cl	4-O Me	H	h
9	2-SO_2NH_2	5-Cl	H	i
10	2-F	3-F	4-F	j
11	2-F	5-CF_3	H	k
12	2-F	3-CF_3	H	l
13	2-O Me	3-Cl	H	m
14	2-Me	3-Cl	H	n
15	3-Cl	4-OH	H	o
16	3-CN	H	H	p
17	*(3) – NCH =	=CH-(4)	H	q

* R^x and R^y together with the carbon atoms in the 3- and 4-position of the phenyl ring, to which they are attached, form a pyrrole ring.

a) ^{1}H NMR Spectrum: (DMSO d_6) 2.07 – 2.16 (m, 1H), 2.29 (s, 3H), 2.42 – 2.58 (m, 2H + DMSO), 2.84 (s, 3H), 3.04 (s, 3H), 3.62 (dd, 1H), 3.71 (t, 1H), 3.93 (s, 3H), 5.12 (m,

1H), 7.20 (s, 1H), 7.43 (t, 1H), 7.69 – 7.76 (m, 2H), 8.05 (dd, 1H), 8.48 (s, 1H), 9.55 (s, 1H); Mass Spectrum: $(M+H)^+$ 474.

b) ^{1}H NMR Spectrum: (DMSO d_6) 2.05 – 2.15 (m, 1H), 2.28 (s, 3H), 2.46 – 2.59 (m, 2H + DMSO), 2.83 (s, 3H), 3.04 (s, 3H), 3.61 (dd, 1H), 3.70 (t, 1H), 3.91 (s, 3H), 5.07 (m, 1H), 6.61 – 6.70 (m, 2H), 7.15 (s, 1H), 7.21 (t, 1H), 7.65 (s, 1H), 8.26 (s, 1H), 9.28 (s, 1H), 9.83 (s, 1H); Mass Spectrum: $(M+H)^+$ 456.16

c) ^{1}H NMR Spectrum: (DMSO d_6) 2.06 – 2.16 (m, 1H), 2.28 (s, 3H), 2.43 – 2.60 (m, 2H + DMSO), 2.84 (s, 3H), 3.05 (s, 3H), 3.61 (dd, 1H), 3.71 (t, 1H), 3.92 (s, 3H), 5.08 (m, 1H), 7.14 (t, 1H), 7.18 (s, 1H), 7.35 (t, 1H), 7.54 (m, 1H), 7.68 (s, 1H), 8.31 (s, 1H), 9.48 (s, 1H); Mass Spectrum: $(M+H)^+$ 458.09

d) ^{1}H NMR Spectrum: (DMSO d_6) 2.05 – 2.16 (m, 1H), 2.28 (s, 3H), 2.47 – 2.60 (m, 2H + DMSO), 2.84 (s, 3H), 3.04 (s, 3H), 3.62 (dd, 1H), 3.72 (t, 1H), 3.93 (s, 3H), 5.10 (m, 1H), 7.13 (m, 1H), 7.20 (s, 1H), 7.35 (m, 1H), 7.50 (m, 1H), 7.70 (s, 1H), 8.38 (s, 1H), 9.57 (s, 1H); Mass Spectrum: $(M+H)^+$ 458.17

e) NMR Spectrum: (DMSO d_6) 2.08 – 2.17 (m, 1H), 2.29 (s, 3H), 2.46 – 2.60 (m, 2H + DMSO), 2.85 (s, 3H), 3.05 (s, 3H), 3.62 (dd, 1H), 3.71 (t, 1H), 3.94 (s, 3H), 5.09 (m, 1H), 7.20 (s, 1H), 7.32 – 7.40 (m, 2H), 7.65 – 7.70 (m, 2H), 8.39 (s, 1H), 9.59 (s, 1H); Mass Spectrum: $(M+H)^+$ 474.11

f) ^{1}H NMR Spectrum: (DMSO d_6) 2.07 – 2.17 (m, 1H), 2.29 (s, 3H), 2.42 – 2.59 (m, 2H + DMSO), 2.83 (s, 3H), 3.04 (s, 3H), 3.61 (dd, 1H), 3.71 (t, 1H), 3.92 (s, 3H), 5.09 (m, 1H), 7.19 (s, 1H), 7.30 – 7.34 (m, 1H), 7.50 – 7.59 (m, 2H), 7.68 (s, 1H), 8.33 (s, 1H), 9.56 (s, 1H); Mass Spectrum: $(M+H)^+$ 474.10

g) ^{1}H NMR Spectrum : (DMSO d_6) 2.07 – 2.18 (m, 1H), 2.29 (s, 3H), 2.40 – 2.50 (m, 2H + DMSO), 2.83 (s, 3H), 3.04 (s, 3H), 3.57 – 3.75 (m, 2H), 3.93 (s, 3H), 5.11 (m, 1H), 6.94 (d, 1H), 7.10 (d, 1H), 7.18 (s, 1H), 7.54 (s, 1H), 7.69 (s, 1H), 8.35 (s, 1H), 9.22 (s, 1H), 10.04 (s, 1H); Mass Spectrum: $(M+H)^+$ 472.06

h) ^{1}H NMR Spectrum: (DMSO d_6) 2.07 – 2.16 (m, 1H), 2.28 (s, 3H), 2.40 – 2.59 (m, 2H + DMSO), 2.86 (s, 3H), 3.04 (s, 3H), 3.59 – 3.72 (m, 2H), 3.87 (s, 3H), 3.93 (s, 3H), 5.12 (m, 1H), 7.15 – 7.20 (m, 2H), 7.64 (d, 1H), 7.76 (s, 1H), 7.84 (s, 1H), 8.40 (s, 1H), 9.43 (s, 1H); Mass Spectrum: $(M+H)^+$ 486.08

i) ^{1}H NMR Spectrum: (DMSO d_6) 2.15 – 2.24 (m, 1H), 2.32 (s, 3H), 2.40 – 2.56 (m, 1H + DMSO), 2.60 – 2.68 (m, 1H), 2.84 (s, 3H), 3.06 (s, 3H), 3.63 – 3.78 (m, 2H), 3.96 (s, 3H), 5.01 (m, 1H), 7.23 (m, 1H), 7.30 – 7.37 (m, 2H), 7.83 – 7.95 (m, 2H), 8.67 (s, 1H), 9.01 (s, 1H); Mass Spectrum: $(M+H)^+$ 535.03

j) ^{1}H NMR Spectrum: (DMSO d_6) 2.08 – 2.17 (m, 1H), 2.28 (s, 3H), 2.42 – 2.61 (m, 2H + DMSO), 2.83 (s, 3H), 3.05 (s, 3H), 3.62 (dd, 1H), 3.72 (t, 1H), 3.93 (s, 3H), 5.08 (m, 1H), 7.20 (s, 1H), 7.32 – 7.40 (m, 2H), 7.67 (s, 1H), 8.35 (s, 1H), 9.68 (s, 1H); Mass Spectrum: $(M+H)^+$ 476.08

k) ^{1}H NMR Spectrum: (DMSO d_6) 2.09 – 2.19 (m, 1H), 2.30 (s, 3H), 2.42 – 2.61 (m, 2H + DMSO), 2.84 (s, 3H), 3.05 (s, 3H), 3.62 (dd, 1H), 3.72 (t, 1H), 3.94 (s, 3H), 5.09 (m, 1H), 7.21 (s, 1H), 7.55 (t, 1H), 7.65 – 7.71 (m, 2H), 7.95 (d, 1H), 8.36 (s, 1H), 9.69 (s, 1H); Mass Spectrum: $(M+H)^+$ 508.07

l) ^{1}H NMR Spectrum: (DMSO d_6) 2.08 – 2.18 (m, 1H), 2.28 (s, 3H), 2.40 – 2.60 (m, 2H + DMSO), 2.84 (s, 3H), 3.04 (s, 3H), 3.61 (dd, 1H), 3.71 (t, 1H), 3.93 (s, 3H), 5.09 (m, 1H), 7.20 (s, 1H), 7.45 (t, 1H), 7.65 (t, 1H), 7.70 (s, 1H), 7.91 (t, 1H), 8.35 (s, 1H), 9.68 (s, 1H); Mass Spectrum: $(M+H)^+$ 508.06

m) ^{1}H NMR Spectrum: (DMSO d_6) 2.07 – 2.17 (m, 1H), 2.28 (s, 3H), 2.42 – 2.60 (m, 2H + DMSO), 2.83 (s, 3H), 3.04 (s, 3H), 3.57 – 3.75 (m, 2H), 3.68 (s, 3H), 3.92 (s, 3H), 5.12 (m, 1H), 7.14 - 7.20 (m, 2H), 7.36 (d, 1H), 7.53 (d, 1H), 7.73 (s, 1H), 8.34 (s, 1H), 9.42 (s, 1H); Mass Spectrum: $(M+H)^+$ 486.07

n) ^{1}H NMR Spectrum: (DMSO d_6) 2.08 – 2.15 (m, 1H), 2.17 (s, 3H), 2.29 (s, 3H), 2.44 – 2.54 (m, 1H + DMSO), 2.57 (dd, 1H), 2.83 (s, 3H), 3.04 (s, 3H), 3.61 (dd, 1H), 3.72 (t, 1H), 3.93 (s, 3H), 5.08 (m, 1H), 7.16 (s, 1H), 7.25 – 7.30 (m, 2H), 7.35 – 7.40 (m, 1H), 7.68 (s, 1H), 8.26 (s, 1H), 9.57 (s, 1H); Mass Spectrum: $(M+H)^+$ 470.09

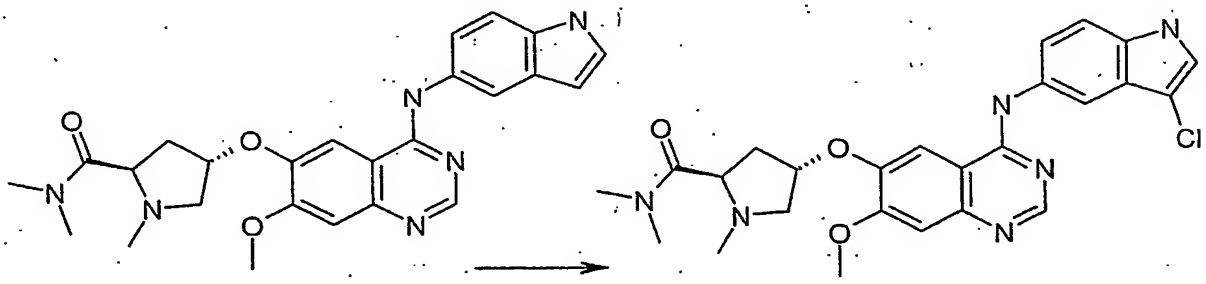
o) ^{1}H NMR Spectrum: (DMSO d_6) 2.07 – 2.15 (m, 1H), 2.29 (s, 3H), 2.40 – 2.58 (m, 2H + DMSO), 2.84 (s, 3H), 3.04 (s, 3H), 3.59 – 3.72 (m, 2H), 3.92 (s, 3H), 5.11 (m, 1H), 6.98 (d, 1H), 7.16 (s, 1H), 7.44 (dd, 1H), 7.69 (s, 1H), 7.71 (d, 1H), 8.38 (s, 1H), 9.37 (s, 1H), 9.94 (s, 1H); Mass Spectrum: $(M+H)^+$ 472.06

p) ^{1}H NMR Spectrum: (DMSO d_6) 2.08 – 2.18 (m, 1H), 2.29 (s, 3H), 2.41 – 2.58 (m, 2H + DMSO), 2.83 (s, 3H), 3.04 (s, 3H), 3.60 – 3.74 (m, 2H), 3.93 (s, 3H), 4.18 (s, 1H), 5.14 (m, 1H), 7.17 – 7.23 (m, 2H), 7.40 (t, 1H), 7.72 (s, 1H), 7.83 (d, 1H), 7.92 (s, 1H), 8.35 (s, 1H), 9.68 (s, 1H); Mass Spectrum: $(M+H)^+$ 446.12

q) ^{1}H NMR Spectrum: (DMSO d_6) 2.06 – 2.17 (m, 1H), 2.28 (s, 3H), 2.40 – 2.58 (m, 2H + DMSO), 2.83 (s, 3H), 3.04 (s, 3H), 3.60 – 3.73 (m, 2H), 3.92 (s, 3H), 5.12 (m, 1H), 6.42 (s, 1H), 7.13 (s, 1H), 7.26 - 7.40 (m, 3H), 7.76 (d, 2H), 8.31 (s, 1H), 9.46 (s, 1H), 11.04 (s, 1H); Mass Spectrum: $(M+H)^+$ 461.12

Example 8

(4*S*)-4-({4-[(3-Chloro-1*H*-indol-5-yl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide



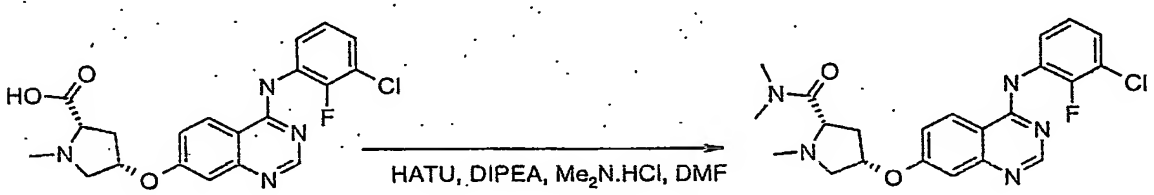
N-Chlorosuccinimide (22 mg) was added to a stirred solution of (4*S*)-4-{[4-(1*H*-indol-5-ylamino)-7-methoxyquinazolin-6-yl]oxy}-*N*,*N*,1-trimethyl-D-prolinamide (**Table 3,**

Compound 17), (77 mg) in DMF (5 ml) at room temperature under an atmosphere of nitrogen and the reaction mixture was stirred for 1 hour.

The reaction mixture was quenched with water and extracted with ethyl acetate. The organics were then adsorbed onto silica and then purified by column chromatography eluting with increasingly polar mixtures of methanol/methylene chloride (0/100-10/90). The desired product fractions were combined, evaporated and triturated with diethyl ether to give (4*S*)-4-({4-[(3-chloro-1*H*-indol-5-yl)amino]-7-methoxyquinazolin-6-yl}oxy)-*N*,*N*,1-trimethyl-D-prolinamide as a cream coloured solid (25 mg). ^{1}H NMR Spectrum: (DMSO d_6) 2.08 – 2.17 (m, 1H), 2.29 (s, 3H), 2.40 – 2.59 (m, 2H + DMSO), 2.85 (s, 3H), 3.05 (s, 3H), 3.60 – 3.73 (m, 2H), 3.92 (s, 3H), 5.14 (m, 1H), 7.16 (s, 1H), 7.41 (d, 1H), 7.48 - 7.52 (m, 2H), 7.75 – 7.77 (m, 2H), 8.36 (s, 1H), 9.52 (s, 1H), 11.32 (s, 1H); Mass Spectrum: $(M+H)^+$ 495.12

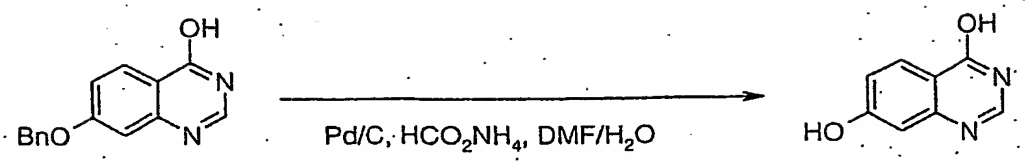
Example 9

(4*S*)-4-({4-[(3-Chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-*N*,*N*,1-trimethyl-L-prolinamide



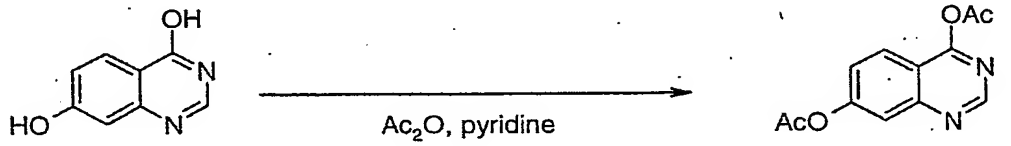
(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-1-methyl-L-proline (150mg, 0.36mmol), diisopropylethylamine (0.31ml, 1.80mmol) and *O*-(7-azabenzotriazol-1-yl)-*N*, *N*, *N'*, *N'*-tetramethyluronium hexafluorophosphate (205mg, 0.54mmol) were dissolved in *N*,*N*-dimethylformamide (2ml) and dimethylamine hydrochloride (44mg, 0.54mmol) added. The mixture was stirred at room temperature for 1.5h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica eluting with methanol/dichloromethane (5/95) to give (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-*N*,*N*,1-trimethyl-L-prolinamide (92mg, 58%) as a white solid. ^{1}H NMR spectrum: (DMSO d_6) 1.81 (m, 1H); 2.21 (s, 3H); 2.59 (dd, 1H); 2.81 (m, 4H); 3.07 (s, 3H); 3.21 (m, 2H); 5.07 (s, 1H); 7.08 (m, 1H); 7.24 (m, 2H); 7.49 (m, 2H); 8.34 (d, 1H); 8.42 (s, 1H); 9.80 (s, 1H). Mass Spectrum: $(MH)^+$ 444.

The starting material was prepared as follows:

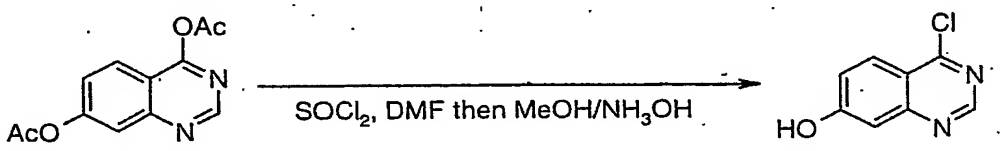


7-(Benzyloxy)quinazolin-4-ol (2.5g, 9.91mmol) was suspended in *N,N*-dimethylformamide (40ml) and the system purged with nitrogen gas. 10% Palladium on carbon (0.63g, 25% by mass) and ammonium formate (6.2g, 99.1mmol) in water (5ml) were added. The mixture was stirred at room temperature for 2h, filtered and concentrated under reduced pressure. The residue was suspended in water, filtered and dried to give quinazoline-4,7-diol (1.08g, 67%) as a white solid.

^{1}H NMR spectrum: (DMSO d_6) 6.95 (m, 2H); 7.95 (m, 2H); 10.42 (brs, 1H); 11.90 (brs, 1H); Mass Spectrum: $(MH)^+$ 163.

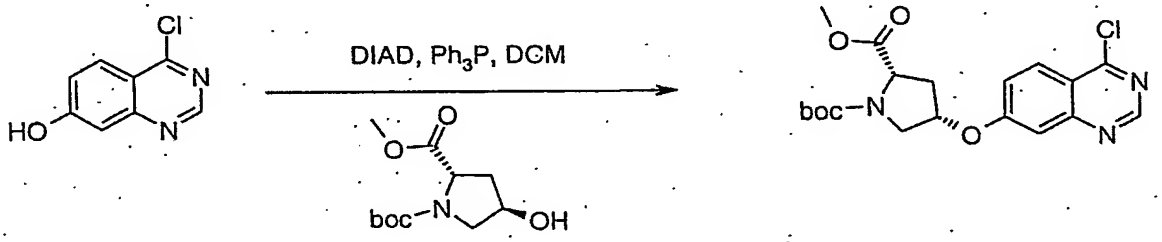


Quinazoline-4,7-diol (1.0g, 6.17mmol) was suspended in acetic anhydride (8ml) and pyridine (1.1ml, 1.42mmol) added. The mixture was heated at reflux for 2.5h, cooled and carefully poured onto ice/water and stirred for 1h. The solid was filtered off and dried to give quinazoline-4,7-diyl diacetate (1g, 79%). ^{1}H NMR spectrum: (DMSO d_6) 2.33 (s, 3H); 2.74 (s, 3H); 7.39 (dd, 1H); 7.49 (d, 1H); 8.26 (d, 1H); 8.62 (s, 1H).

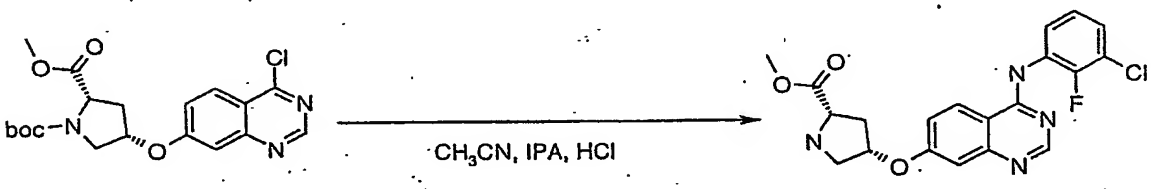


Quinazoline-4,7-diyl diacetate (1.0g, 4.89mmol) and *N,N*-dimethylformamide (a few drops) were heated in thionyl chloride (12ml) at reflux for 3h. The mixture was cooled, concentrated under reduced pressure and the system azeotroped with toluene. The residue was dissolved in dichloromethane (6ml) and carefully added to methanol (8ml) and

concentrated aqueous ammonia solution (1.5ml) and stirred for 2h. The mixture was concentrated under reduced pressure and the solid suspended in water, filtered and dried to give 4-chloroquinazolin-7-ol (655mg, 74%) as a white solid. ^{1}H NMR spectrum: (DMSO d_6) 7.23 (d, 1H); 7.37 (dd, 1H); 8.12 (d, 1H); 8.87 (s, 1H); 11.22 (brs, 1H); Mass Spectrum: $(MH)^+$ 181.

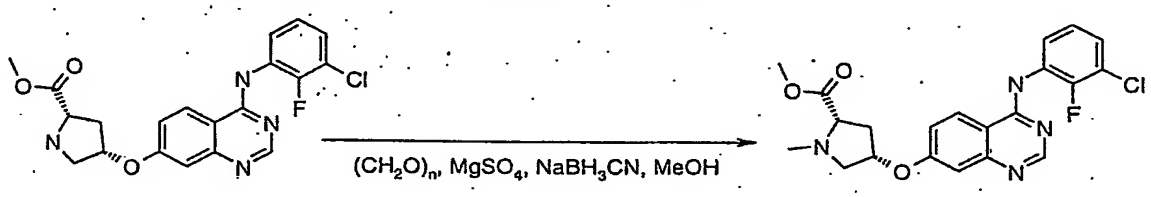


4-Chloroquinazolin-7-ol (0.64g, 3.54mmol), (2S,4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (1.04g, 4.25mmol) and triphenylphosphine (1.11g, 4.25mmol) were stirred in dichloromethane (30ml) and diisopropyl azodicarboxylate (0.84ml, 4.25mmol) was slowly added. The mixture was stirred at room temperature for 1.75h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica eluting with increasingly polar mixtures of isohexane/ethyl acetate (2/1 to 1/1) to give (2S, 4S)-4-(4-chloro-quinazolin-7-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (1.09g, 75%) as a viscous oil. ^{1}H NMR spectrum: (DMSO d_6) 1.37 (m, 9H); 2.29 (d, 1H); 2.71 (m, 1H); 3.53 (m, 1H); 3.63 (m 3H); 3.87 (m, 1H); 4.47 (m, 1H); 5.35 (m, 1H); 7.32 (m, 1H); 7.46 (s, 1H); 8.17 (d, 1H); 8.98 (s, 1H); Mass Spectrum: $(MH)^+$ 408.

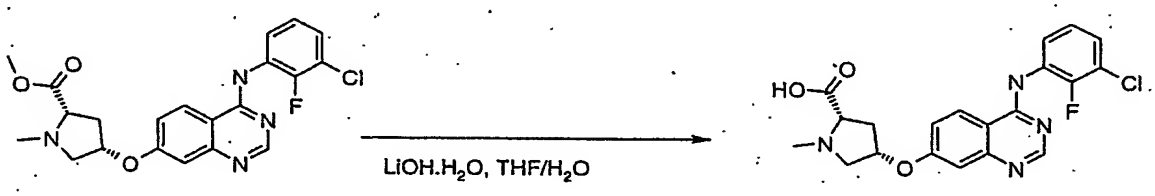


(2S,4S)-4-(4-Chloro-quinazolin-7-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (1.0g, 2.45mmol) and 3-chloro-2-fluoroaniline (323µl, 2.94mmol) were stirred in acetonitrile (25ml) and hydrogen chloride (736µl of a 4M solution in dioxane, 2.94mmol) was added. The mixture was heated at reflux for 2h, cooled and concentrated under reduced pressure. The residue was dissolved in methanol, absorbed onto and Isolute®

SCX column, washed with methanol and eluted with 7N ammonia in methanol. Appropriate fractions were combined and evaporated and the crudes purified by column chromatography on silica eluting with 7N ammonia in methanol/dichloromethane (2/98) to give methyl (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-L-prolinate (811mg, 79%) as a white solid. ^{1}H NMR spectrum: (DMSO d_6) 2.09 (m, 1H); 2.54 (m, 1H); 2.80 (brs, 1H); 3.15 (m, 2H); 3.64 (s, 3H); 3.81 (dd, 1H); 5.11 (m, 1H); 7.16 (m, 2H); 7.28 (t, 1H); 7.51 (m, 2H); 8.35 (d, 1H); 8.44 (s, 1H); 7.80 (s, 1H); Mass Spectrum: $(MH)^+$ 417.



Methyl (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-L-prolinate (50mg, 1.20mmol) was dissolved in methanol (20ml) and magnesium sulphate (289mg, 2.40mmol), paraformaldehyde (360mg, 12.0mmol) and sodium cyanoborohydride (302mg, 4.80mmol) added. The mixture was heated at 50°C for 2.5h, cooled, filtered and evaporated. The crudes were purified by column chromatography on silica eluting with methanol/dichloromethane (2/98) to give methyl (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-1-methyl-L-prolinate (328mg, 63%) as a white solid. ^{1}H NMR spectrum: (DMSO d_6) 2.08 (m, 1H); 2.38 (s, 3H); 2.75 (dd, 1H); 2.86 (m, 1H); 3.13 (t, 1H); 3.26 (d, 1H); 3.71 (s, 3H); 5.15 (m, 1H); 7.15 (d, 1H); 7.28 (dd, 1H); 7.34 (t, 1H); 7.56 (m, 2H); 8.41 (d, 1H); 8.50 (s, 1H); 9.85 (s, 1H); Mass Spectrum: $(MH)^+$ 431.



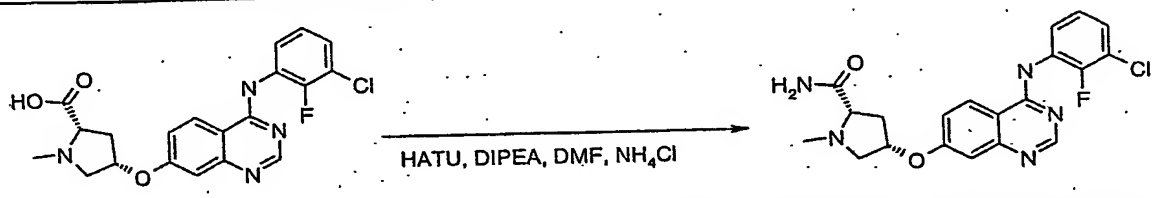
Methyl (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-1-methyl-L-prolinate (325mg, 0.75mmol) was dissolved in tetrahydrofuran (6ml) and water (3ml) and lithium hydroxide monohydrate (158mg, 3.77mmol) added. The mixture was stirred at room temperature for 2h, neutralised with hydrogen chloride (0.95ml of a 4M solution in dioxane, 3.77mmol) and concentrated under reduced pressure. The residue was dissolved in methanol, absorbed onto an Isolute® SCX column, washed with methanol and eluted with 7N ammonia

in methanol. Fractions containing the desired product were combined and evaporated to give (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-1-methyl-L-proline (318mg, 100%) as a white solid.

^{1}H NMR spectrum: (DMSO d_6) 2.00 (m, 1H); 2.35 (s, 3H); 2.66 (m, 2H); 2.82 (t, 1H); 3.24 (d, 1H); 5.03 (m, 1H); 7.06 (m, 1H); 7.17 (dd, 1H); 7.25 (dt, 1H); 7.48 (m, 2H); 8.38 (m, 2H); 10.00 (brs, 1H); Mass Spectrum: $(MH)^+$ 417.

Example 10

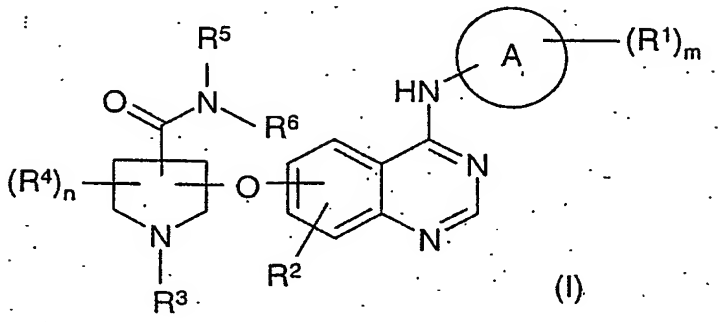
(4*S*)-4-({4-[(3-Chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-1-methyl-L-prolinamide triflouroacetic acid salt



(4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-1-methyl-L-proline (150mg, 0.36mmol), diisopropylethylamine (0.31ml, 1.80mmol) and *O*-(7-azabenzotriazol-1-yl)-*N*, *N*, *N'*, *N'*-tetramethyluronium hexafluorophosphate (205mg, 0.54mmol) were dissolved in *N*,*N*-dimethylformamide (2ml) and ammonium chloride (29mg, 0.54mmol) added. The mixture was stirred at room temperature for 1.5h and then concentrated under reduced pressure. The residues were purified by column chromatography on silica eluting with methanol/dichloromethane(5/95) followed by reverse phase preparative HPLC to give (4*S*)-4-({4-[(3-chloro-2-fluorophenyl)amino]quinazolin-7-yl}oxy)-1-methyl-L-prolinamide triflouroacetic acid salt (92mg, 58%) as a white solid. ^{1}H NMR spectrum: (DMSO d_6) 1.96 (m, 1H); 2.36 (s, 3H); 2.72 (dd, 1H); 2.81 (m, 2H); 3.23 (s, 1H); 3.32 (d, 1H); 5.16 (s, 1H); 7.15 (m, 2H); 7.26 (m, 2H); 7.33 (t, 1H); 7.56 (m, 2H); 8.41 (d, 1H); 8.49 (s, 1H); 9.85 (s, 1H); Mass Spectrum: $(MH)^+$ 416.

CLAIMS

1. A quinazoline derivative of the Formula (I):



(I)

wherein:

either R^2 is in the 6-position and the substituted-pyrrolidinyloxy group is in the 7-position of the quinazoline ring or R^2 is in the 7-position and the substituted-pyrrolidinyloxy group is in the 6-position of the quinazoline ring;

A is phenyl or pyridyl;

each $\mathbf{R^1}$ is a substituent on a ring carbon atom in ring A and is independently selected from halogeno, cyano, nitro, hydroxy, carboxy, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkoxycarbonyl, ureido, N-(1-6C)alkylureido, N,N-di-[(1-6C)alkyl]ureido, $-NR^aR^b$, $-SO_2NR^aR^b$ and a group of the formula $-CONR^aR^b$ (wherein $\mathbf{R^a}$ is hydrogen or (1-6C)alkyl and $\mathbf{R^b}$ selected from hydrogen, (1-6C)alkyl, phenyl, benzyl, heterocyclyl, heterocyclyl(1-3C)alkyl, heteroaryl, heteroaryl(1-3C)alkyl, (3-7)cycloalkyl and (3-7)cycloalkyl(1-3C)alkyl wherein any alkyl, heterocyclyl, heteroaryl and cycloalkyl groups in R^a and R^b are optionally substituted by 1, 2 or 3 substituents selected from (1-4C)alkyl, halogeno, hydroxy and (1-4C)alkoxy;

or $\mathbf{R^a}$ and $\mathbf{R^b}$ together with the nitrogen atom to which they are attached form a 4, 5 or 6-membered ring which optionally contains an additional ring heteroatom selected from nitrogen, oxygen and sulphur and which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from halogeno, hydroxy, (1-4C)alkyl and

(1-3C)alkylenedioxy and optionally substituted on any available ring nitrogen by a substituent selected from (1-4C)alkyl and (2-4C)alkanoyl (provided the ring is not thereby quaternised), and wherein any (1-4C)alkyl or (2-4C)alkanoyl group present as a substituent on the ring formed by R^a and R^b together with the nitrogen atom to which they are attached is optionally substituted by 1, 2 or 3 substituents independently selected from halogeno, hydroxyl, (1-4C)alkyl and (1-4C)alkoxy;)

or, when two $\mathbf{R^1}$ groups are attached to adjacent carbon atoms, they may, together with the carbon atoms to which they are attached, form a pyrrole ring, wherein the pyrrole ring is optionally substituted by 1 or 2 substituents independently selected from (1-6C)alkyl, halogeno, cyano, nitro, hydroxy, amino, carbamoyl, sulfamoyl and trifluoromethyl;

or, when two $\mathbf{R^1}$ groups are attached to adjacent carbon atoms, they may, together form a (1-3C)alkylenedioxy group;

m is 0, 1, 2 or 3;

each $\mathbf{R^2}$ is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-3C)alkyl and a group of the formula R^7O-, wherein R^7 is (1-6C)alkyl optionally substituted by 1, 2 or 3 substituents independently selected from hydroxy and a group of the formula R^8O- (wherein R^8 is (1-3C)alkyl);

$\mathbf{R^3}$ is selected from hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-3C)alkyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (2-6C)alkanoyl, carbamoyl(1-6C)alkyl, N-(1-6C)alkylcarbamoyl(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl(1-6C)alkyl, sulfamoyl(1-6C)alkyl, N-(1-6C)alkylsulfamoyl(1-6C)alkyl, N,N-di-[(1-6C)alkyl]sulfamoyl(1-6C)alkyl and (2-6C)alkanoyl(1-6C)alkyl,

and wherein any (1-6C)alkyl or (2-6C)alkanoyl group within R^3 is optionally substituted by 1, 2 or 3 substituents independently selected from halogeno, hydroxy and (1-6C)alkyl and/or optionally a substituent selected from cyano, nitro, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy and NR^cR^d, wherein $\mathbf{R^c}$ is hydrogen or (1-4C)alkyl and $\mathbf{R^d}$ is hydrogen or (1-4C)alkyl, and wherein any (1-4C)alkyl in R^c or R^d is optionally substituted by 1, 2 or 3 substituents independently selected from halogeno and hydroxy and/or optionally a substituent selected from cyano, nitro and (1-4C)alkoxy,

or $\mathbf{R^c}$ and $\mathbf{R^d}$ together with the nitrogen atom to which they are attached form a 4, 5 or 6 membered ring which optionally contains an additional ring heteroatom selected from

nitrogen, oxygen and sulphur and which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from halogeno, hydroxy, (1-4C)alkyl and (1-3C)alkylenedioxy, and optionally substituted on any available ring nitrogen by a substituent selected from (1-4C)alkyl and (2-4C)alkanoyl (provided the ring is not thereby quaternised),

and wherein any (1-4C)alkyl or (2-4C)alkanoyl group present as a substituent on the ring formed by R^c and R^d together with the nitrogen atom to which they are attached is optionally substituted by 1, 2 or 3 substituents independently selected from halogeno and hydroxy and/or optionally a substituent selected from (1-4C)alkyl and (1-4C)alkoxy;

each R^4 is independently selected from (1-4C)alkyl, (1-4C)alkoxy, cyano, halogeno, hydroxyl and oxo;

n is 0, 1 or 2;

R^5 is hydrogen or (1-6C)alkyl;

R^6 is selected from hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (3-7)cycloalkyl, (C1-6)alkylsulfonyl, heterocyclyl, heteroaryl, (3-7)cycloalkyl(1-3C)alkyl, (3-7)heterocyclyl(1-3C)alkyl and heteroaryl(1-3C)alkyl,

and wherein any (1-3C)alkyl, (1-6C)alkyl, (3-7)cycloalkyl, heteroaryl or heterocyclyl group within R^5 or R^6 is optionally substituted (on any available carbon atoms) by 1, 2 or 3 substituents independently selected from halogeno, hydroxy(1-6C)alkyl, (1-6C)alkoxycarbonyl, carbamoyl, (2-6C)alkanoylamino and hydroxy and/or optionally a substituent selected from oxo, cyano, nitro and (1-4C)alkoxy,

and wherein any heterocyclyl group within R^6 is optionally substituted on any available ring nitrogen (provided the ring is not thereby quaternised) by (1-4C)alkyl or (2-4C)alkanoyl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 4, 5 or 6 membered ring which is optionally substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from halogeno, hydroxy, (1-4C)alkyl and (1-3C)alkylenedioxy, and optionally substituted on any available ring nitrogen by a substituent selected from (1-4C)alkyl and (2-4C)alkanoyl (provided the ring is not thereby quaternised),

and wherein any (1-4C)alkyl or (2-4C)alkanoyl group present as a substituent on the ring formed by R^5 and R^6 together with the nitrogen atom to which they are attached is optionally substituted by 1, 2 or 3 substituents independently selected from halogeno and hydroxy and/or optionally a substituent selected from (1-4C)alkyl and (1-4C)alkoxy;

provided that when the pyrrolidinyloxy group is linked to the 6-position of the quinazoline ring, m is 2 and substituents R^1 are both halogeno and attached to the 2- and 3- positions of the ring A, then R^6 is selected from substituted-(1-6C)alkyl (wherein substituted-(1-6C)alkyl is (1-6C)alkyl substituted by 1, 2 or 3 substituents independently selected from halogeno, hydroxy(1-6C)alkyl, (1-6C)alkoxycarbonyl, carbamoyl, (2-6C)alkanoylamino and hydroxy and/or optionally a substituent selected from oxo, cyano, nitro and (1-4C)alkoxy), (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (3-7)cycloalkyl, (C1-6)alkylsulfonyl, (3-7)heterocyclyl, heteroaryl, (3-7)cycloalkyl(1-6C)alkyl, (3-7)heterocyclyl(1-6C)alkyl and heteroaryl(1-6C)alkyl,

and wherein any (3-7)cycloalkyl, heteroaryl or (3-7)heterocyclyl group within R^5 or R^6 is optionally substituted (on any available carbon atoms) by 1, 2 or 3 substituents independently selected from halogeno, hydroxy(1-6C)alkyl, (1-6C)alkoxycarbonyl, carbamoyl, (2-6C)alkanoylamino and hydroxy and/or optionally a substituent selected from oxo, cyano, nitro and (1-4C)alkoxy,

and wherein any heterocyclyl group within R^6 is optionally substituted on any available ring nitrogen (provided the ring is not thereby quaternised) by (1-4C)alkyl or (2-4C)alkanoyl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 4, 5 or 6 membered ring which is substituted by 1 or 2 substituents on an available ring carbon atom, independently selected from (1-3C)alkylenedioxy;

or a pharmaceutically-acceptable salt thereof.

2. A pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined in claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

3. A quinazoline derivative of the Formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use as a medicament.

4. The use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal.

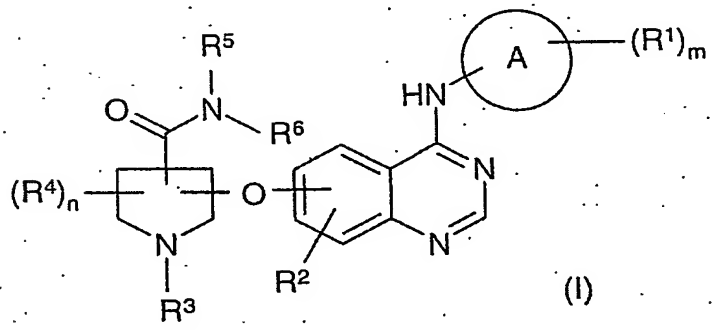
5. A method for producing an anti-proliferative effect in a warm-blooded animal in need of such treatment, which comprises administering to, said animal a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt thereof, as defined in Claim 1.

5

A B S T R A C T

TITLE : QUINAZOLINE DERIVATIVES

The invention concerns a quinazoline derivative of the Formula (I):



(I)

wherein each of the variables have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an antiproliferative agent in the prevention or treatment of tumours which are sensitive to inhibition of erbB receptor tyrosine kinases.